Interpersonal mechanisms in recurrence of depression

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General introduction

1 RECURRENCE OF DEPRESSION

One of the greatest problems with major depressive disorder is that it is a highly recurrent disease. About 50% of patients recovered from an episode of major depression will suffer another episode once in their life (Belsher and Costello, 1988). The picture is even worse for patients who have been depressed already a number of times, as risk of recurrence seems to increase progressively with each successive episode (Bauer et al., 2002; Kessing et al., 2004). On the other hand, recurrence rates progressively decrease as the duration of recovery increases (Belsher and Costello, 1988; Solomon et al., 2000). These observations point to the relevance of identifying mechanisms involved in recurrence of depression, as these may be targeted upon to help remitted patients to remain well.

Despite a widespread agreement that complex mental illnesses, such as depression, are heterogeneous in their etiology and course (Bebbington, 1987; Costello et al., 2002), theory and research aimed at identifying risk factors for (recurrence of) depression are predominantly monodimensional in nature. Factors from single fields of research are usually studied in isolation, and attempts to integrate findings are rare. Studies that simultaneously investigate factors belonging to different fields are needed for a multifactorial account of depression (Costello et al., 2002). The study described in this thesis was designed in this way.

The research fields focused upon in the present study are: personality, social cognition, interpersonal behavior, stress physiology, and interpersonal stress. The study centers around an intriguing concept from the field of personality, neuroticism. Neuroticism is a personality construct that is very consistently related to depression (and several other kinds of distress). At the same time, it is rather unclear what this construct actually is and how it confers risk of depression. In this thesis, we investigate how neuroticism is linked to recurrence of depression by examining potentially intermediating factors from the 4 other fields of depression research. We study these factors in patients whose depression is in remission.

The specific factors under investigation were chosen from an interpersonal perspective. This was done because the social realm is inextricably bound up with depression (Joiner and Coyne, 1999; Rhodes and Lakey, 1999), and presumably particularly so when the disease has taken a recurrent course (Coyne, 1999). We expect that interpersonal factors also play an important

role in the mechanisms linking neuroticism to recurrence of depression.

In the following section, we introduce the 5 research fields of our interest and the factors we selected from these fields to investigate. In section 3, we review what is known about the interrelationships between factors from these different fields. On the basis of this literature, we subsequently formulate our hypotheses on how the factors under investigation are related to recurrence of depression and how their combined action may explain the risk associated with neuroticism (section 4).

2 FIVE FIELDS OF INVESTIGATION

The 5 fields that are focused upon in this thesis are all widely studied in the context of depression. We will outline how these fields are implicated in depression theory and research, and introduce the potential risk factors of recurrence that were investigated in the present study.

2.1 Personality

Personality refers to an individual's characteristic patterns of thinking, feeling, and behaving (Klein, 2002). Most contemporary models of personality distinguish a small number of higher-order personality dimensions (e.g., the "Big Five", McCrae and Costa, 1999), each of which is subdivided into a larger number of lower-order traits or "facets". Neuroticism is one of the higher-order personality dimensions included in all major models of personality. Neuroticism has been defined as "a stable, heritable, and highly general trait dimension with a multiplicity of aspects ranging from mood to behavior (...) the core of which is a temperamental sensitivity to negative stimuli" (Clark et al., 1994), or as "a broad dimension of individual differences in the tendency to experience negative, distressing emotions and to possess associated behavioral and cognitive traits" (Costa and McCrae, 1987). These widely used definitions of neuroticism nicely illustrate the indeterminate character of the concept. It comprises an assemblage of aspects as divers as emotional instability, irritability, stress reactivity, fearfulness, the tendency to worry, to be moody, to feel guilty and lonely. These aspects are usually assessed by means of a range of items on a questionnaire, which are taken together to make up the "neuroticism score". This has led to uncertainty as to what neuroticism actually is and how much explanatory value the concept has (e.g., Claridge and Davis, 2001; Ormel et al., 2004c).

Despite the indistinctness of the concept (or probably: *due to* its indistinctness), a great variety of clinical phenomena, both somatic and psychiatric, has been found to be associated with neuroticism (Claridge and Davis, 2001; Neeleman et al., 2002; Neeleman et al., 2004). Depressive disorder is one of the diseases showing very consistent associations with neuroticism. Levels of neuroticism are higher in depressed individuals compared to healthy controls and population samples, and high neuroticism is related to more severe episodes and to a poorer course (Enns and Cox, 1997; Klein, et al., 2002). It is clear that neuroticism has a strong state-dependent component; neuroticism levels decrease as depressive symptoms abate (Klein, et al., 2002). A number of studies, however, have reported that neuroticism scores are still higher in remitted individuals compared to control or population samples (Barnett and Gotlib, 1988; Klein, et al., 2002). Results are not entirely consistent in this respect, but this may have to do with sample selection effects (Barnett and Gotlib, 1988; Klein, et al., 2002). There are more reasons, however, to assume that neuroticism is not only a concomitant of the depressed state, but also confers risk for the development of depressive episodes. First, premorbidly assessed neuroticism is predictive of the onset of depression (Enns and Cox, 1997; Klein, et al., 2002; Ormel et al., 2004b). Secondly, neuroticism measured in remission is predictive of subsequent relapse and recurrence (Marks et al., 1992; Surtees and Wainwright, 1996; Mulder, 2002).

To conclude, neuroticism is a very reliable, but rather non-specific correlate and predictor of (recurrence of) depression. In this thesis we try to give this broad personality construct some hands and feet by concurrently investigating factors from other fields of depression research, which may figure as a link between neuroticism and depression.

2.2 Social cognition

Cognitive research in depression has been influenced greatly by the theory of Aaron Beck (Beck, 1967; Beck et al., 1985). Central to this theory is the concept of the cognitive *schema*. Cognitive schemas are stable underlying structures that guide the perception, integration, interpretation, and retrieval of information. The schemas of particular concern to Beck's theory are those containing negative information about the self and the self in relation to others. These negative schemas are postulated to be developed early in life in response to certain situations and to be later activated by (certain types of) stressful life events. Once activated, these schemas bring about systematic

biases and distortions in the processing of information. Specifically, these biases and distortions are thought to lead to overly pessimistic views of the self, the future, and the world (the "negative cognitive triad"). These, in turn, lead to sadness and the other symptoms of depression.

Since the emergence of Beck's theory (and other important cognitive theories of depression, e.g., Higgins, 1987; Teasdale, 1988; Abramson et al., 1989), a mass of empirical research has shown that depressives do indeed have cognitive distortions and negative biases (Mathews and MacLeod, 1994; Weary and Edwards, 1994; Williams et al., 1997; Alloy et al., 1999; Mineka and Gilboa, 1998). Much of this research, however, suggests that these dysfunctional cognitions are secondary to the depressed mood, disappearing when the depression is over (Barnett and Gotlib, 1988; Persons and Miranda, 1992). Yet, there is also some evidence of the presence of cognitive distortions and biases before onset of the depression or after recovery (Alloy et al., 1999; Austin et al., 2001; Rude et al., 2002). Moreover, it is not sure whether the negative findings in remitted samples refute the proposed *causal* role of cognition in depression. Dysfunctional cognitions may be inaccessible to measurement outside of the depressive episode because they might need to be primed by negative mood or activated by stressful experiences (Segal and Ingram, 1994; Miranda and Gross, 1997; Just et al, 2001).

The field of *social* cognition concerns the cognitive processing of *social* information. The present study focuses on the perception part of social cognition, in particular the perception of emotions from facial and vocal expressions. Emotional expressions play an important role in human communication (Burgoon, 1985; Darwin, 1998), and the accurate decoding of emotional cues is quite essential to social functioning. Misidentification of emotional expressions may lead to interpersonal problems, and thus contribute to the experience of interpersonal stress and the erosion of social supportive resources. Moreover, a negatively biased emotion perception may promote pessimistic views of the self and (one's relationships with) others. In these ways, deficits in emotion perception may increase the risk of depression (Hammen, 1992; Gotlib et al., 2004).

Empirical studies on emotion perception of depressives most often concern the decoding of facial expressions. A few studies are done on emotions expressed in tone of voice. Both lines of research show evidence of perceptual deficits in depressed patients. Depressives are found to be *impaired* in emotion recognition; i.e. they make more errors than controls in the identification

of emotional expressions (Feinberg et al., 1986; Zuroff and Colussy, 1986; Murphy and Cutting, 1990; Persad and Polivy, 1993; Mikhailova et al., 1996; Emerson et al. 1999; Leppanen et al., 2004; Luck and Dowrick, 2004; Surguladze et al., 2004) (but see also some negative findings: Walker et al., 1984; Archer et al., 1992; Gaebel and Wolwer, 1992; Ridout et al., 2003). Depressives are also found to have a *negative bias* in emotion perception, i.e. they show increased attention to and enhanced recall of negative expressions vs. other expressions (Gilboa-Schechtman et al., 2002; Ridout et al., 2003; Gotlib et al., 2004), and they interpret emotional expressions in a more negative (or less positive) way than controls do (Gur et al., 1992; Hale et al., 1998; Leppanen et al., 2004; Luck and Dowrick, 2004; Surguladze et al., 2004). Such a negative perceptual bias has been shown to be related to a poor course of the depression (Bouhuys et al., 1999a; Geerts and Bouhuys, 1998). A few studies with assessments done both in depression and in remission showed that perceptual deficits tend to diminish when patients recover (Mikhailova et al., 1996; Bouhuys et al., 1999b; Levkovitz et al., 2003). One of these studies also related emotion perception of remitted patients to subsequent relapse (Bouhuys et al., 1999b). This study found that higher levels of negative emotions perceived in facial expressions were associated with a higher risk of relapse.

2.3 Interpersonal behavior

In response to Beck's theory, which seeks the origins of depression exclusively "inside the head" of the individual, theories have emerged that stress the importance of interpersonal interactions in depression. The best known of these approaches is James Coyne's interactional theory of depression (Coyne, 1976). This theory holds that depression-prone persons, because of their behavior, elicit negative reactions from others that serve to exacerbate depressive symptomatology. Specifically, it proposes that the depression-prone person seeks reassurance from others when feeling distressed, insecure, or worthless. Other people may provide reassurance, but the depression-prone person doubts its genuineness, for example because he or she thinks that they act from pity or obligation, or because the verbal messages do not correspond with the nonverbal ones. This leads the depression-prone person again to seek reassurance. A repetitive pattern is established, in which increasing demands for reassurance are made. As a result, others become annoyed and irritated, or even distressed themselves. This increases the likelihood that they will reject

and avoid the depression-prone person, which adds to the deterioration of this person's self-concept and the disruption of his or her social network, leading to exacerbation or maintenance of depressive symptoms.

Although Coyne's theory as formulated in his 1976 article was in important respects vague and underdeveloped (Coyne, 1999), it has provoked a lot of empirical work on the interpersonal context of depression. This research has confirmed that depressed individuals elicit rejection from others (at least in the long term), and that they often experience dissatisfactory or disrupted relationships (Marcus and Nardone, 1992; Segrin, 1998). There is also evidence for excessive reassurance seeking in depressed patients, and a few studies show that this interaction style indeed predicts longitudinal increases in depressive symptoms (Joiner, 2000). The literature further points to various other problems in depressives' interpersonal behavior, such as showing overly dependent or clinging behavior, talking about self-focused or negative issues, and having poor conflict-resolution skills (Gotlib and Hammen, 1992; Segrin, 1998; Joiner, 2002).

The interpersonal behavior of depressives is also unfavorable in several of its *nonverbal* aspects (Segrin, 1998; Segrin, 2000; Joiner, 2002). Nonverbal cues are very powerful elements of human communication (Burgoon, 1985; Depaulo and Friedman, 1998), notwithstanding the fact that people are often not consciously aware of them. Empirical evidence substantiates that the greater part of the meaning in face-to-face interchanges is communicated nonverbally (Burgoon, 1985). Research also shows that people tend to place greater reliance on nonverbal than on verbal cues, especially when nonverbal signals conflict with the verbal message (Burgoon, 1985). Given the importance of nonverbal signals in interpersonal communication, the observation that depressed patients show deviant nonverbal behavior is quite relevant. Depressives often exhibit a behavioral pattern of low interpersonal involvement, unresponsiveness, and negativity. They tend to speak slowly, with little volume and long pauses, gaze little at their interaction partners, gesture and head-nod infrequently, and exhibit sad facial expressions (Segrin, 1998; Segrin, 2000). Many of these behaviors are correlated with aversion and rejection from others (Gotlib and Hammen, 1992; Segrin and Abramson, 1994). Whether such behaviors are also *causal* to the depression is not clear. The longitudinal studies done to examine this have yielded mixed results thus far (Bouhuys et al., 1991; Bouhuys and Van den Hoofdakker, 1993; Troisi et al., 1989; Segrin, 2000; Joiner, 2002).

Most studies on the interpersonal behavior of depressed or depression-

prone individuals are one-sided; they focus on either the behavior of these individuals or that of their interaction partners. The strong point of Coyne's interactional theory has been that it paid attention to the *interplay* between the behaviors of the people concerned. Particularly relevant in this regard is the observation that interaction partners usually adjust their behaviors to each other. They automatically adopt each other's postures, movements, facial expressions, speech patterns, rhythms, and mannerisms (Bernieri and Rosenthal, 1991; Burgoon et al., 1993; Cappella, 1996; Lakin et al., 2003). Such behavioral matching and synchronization processes are a characteristic feature of everyday interactions and can be observed already at a very young age (Condon and Sander, 1974; Isabella et al., 1989). They are thought to be a fundamental element of human communication, serving to promote harmonious relationships, as a kind of "social glue" (Kendon, 1970; Chartrand and Bargh, 1999). This thought is corroborated by evidence that interactions characterized by a high degree of behavioral symmetry and synchrony are experienced as pleasant, supportive, and rewarding (Tickle-Degnen and Rosenthal, 1990; Bernieri and Rosenthal, 1991; Cappella, 1997), and that interaction partners who are "in sync" or "in tune" with one another report high feelings of attraction and affiliation (Cappella and Palmer, 1990). Two studies of our own research group showed that mutual adjustment of nonverbal behavior is also related to a favorable course of depression. The degree to which depressed patients and their experimental conversation partners adjusted their levels of nonverbal involvement behavior to each other was predictive of the subsequent improvement of the patients' depression (Geerts et al., 1996, 2000).

The above reviewed findings and ideas prompted us to investigate whether mutual adjustment of nonverbal behavior also plays a role in recurrence of depression. A lack of nonverbal "match" during social interactions presumably increases the likelihood that interactions become dissatisfactory and stressful, and that interaction partners eventually withdraw. Interpersonal stress and shrinkage of the social network, in turn, increase the risk of recurrence of depression (Paykel, 1994).

2.4 Stress physiology

The term "stress" is generally used in two ways: to identify events or circumstances that are perceived as being adverse ("stressors") or to describe the state induced by such events or circumstances (the "stress reaction"). This section deals with the latter.

The physiological system that plays a key role in the stress reaction is the hypothalamic-pituitary-adrenal (HPA) axis. During a perceived physical or psychological threat, a cascade of hormones is released from this axis. First, corticotropin releasing factor (CRF) is released from the hypothalamus. CRF subsequently triggers the release of adrenocorticotropin hormone (ACTH) from the pituitary gland into the bloodstream. Finally, ACTH stimulates the release of corticosteroids (cortisol) from the adrenal cortex. The "stress hormone" cortisol brings about a variety of physiological, cognitive, and behavioral changes that are critical for successful adaptation to the stressor (Sapolsky et al., 2000; Erickson et al., 2003). It also serves to down-regulate the stress response, inhibiting further release of CRF and ACTH. This negative feedback mechanism prevents the system from overshooting (Sapolsky et al., 2000).

Whereas activation of the HPA axis is an essential part of a normal response to stress, prolonged or excessive HPA-axis activation is almost always deleterious (McEwen, 2000; Wolkowitz et al., 2001). Hyperactivity of the HPA axis is also related to psychopathology. Elevated cortisol levels and impaired feedback inhibition of the stress system are the most widely replicated biological abnormalities in major depression (Thase and Howland, 1995; Wolkowitz et al., 2001). This is not to say that HPA-axis dysregulations are unique to depression or that they can be found invariably in depressives (e.g., Thase et al., 2002; Strickland et al., 2002). But the association between depression and hypercortisolism is evident enough to have reached the status of textbook truism (Cowen, 2002).

Many authors consider HPA-axis hyperactivity to be a state effect of the depression, as it usually resolves upon remission (Thase and Howland, 1995). A number of studies, however, show that HPA-axis hyperactivity may persist after apparent clinical recovery and that the individuals concerned are at a higher risk of subsequent relapse and recurrence (Gurguis et al., 1990; Ribeiro et al., 1993; Zobel et al., 1999; Holsboer, 2001; Zobel et al., 2001). Besides, there are other indications that dysregulations in HPA-axis functioning may also be causal to the development of depressive episodes. Three lines of evidence are relevant in this respect. First, substantial evidence from a variety of studies suggests that having been exposed to stress early in life represents a major risk for the development of depression (Heim and Nemeroff, 2001). Secondly, animal research has convincingly demonstrated that early stress (either pre- or postnatal) and deprived caregiving conditions lead to perma-

nent changes in the stress system, resulting in a long-lasting hyperactivity and sensitization of the HPA axis, thus increasing susceptibility to stress later in life (Weinstock, 1997; Kaufman et al., 2000). A number of clinical studies have extended these findings to humans (Heim and Nemeroff, 2001; Meyer et al., 2001). Thirdly, it is well established that the onset of depressive disorder is often precipitated by stressful life events or chronic difficulties (see below). Together, these lines of evidence suggest that adverse experience during early development may lead to hypersensitivity of the stress system, predisposing these individuals to the development of depression (Post and Weiss, 1998; McEwen, 2000; Meyer et al., 2001).

2.5 Interpersonal stress

The importance of interpersonal stress in the etiology of depression has come to the fore a number of times already in the above sections. "Interpersonal stress" does not refer to a clearly defined research field, but the concept plays a key role in several interpersonal approaches of depression (see Hammen, 1999). It figures throughout this thesis as a factor of special relevance to our understanding of recurrence of depression. Our measure of interpersonal stress is the occurrence of stressful life events during the follow-up of our study, in particular life events in which interpersonal interactions play a role (e.g., divorce).

Stressful life events (traditionally defined as "objective experiences that are sufficiently disruptive or threatening as to require a substantial readjustment on the part of the individual" (Cronkite and Moos, 1995)) have long been implicated in depression. The work of George Brown has been very influential to this research. Brown showed that severe life events, often involving loss and disappointments in close relationships, had a crucial role in the precipitation of depression, and he also pointed to the relevance of the social context in which stressful life events occur (Brown and Harris, 1978; Brown, 1993). By now, there is a large body of literature showing that exposure to stressful life events is associated with the subsequent onset of depressive episodes (Brown and Harris, 1989; Kessler, 1997; Paykel, 2003). Because of the consistency of this association, the common notion is that stressful life events trigger or provoke depression.

Stressful life events have also been found to be predictive of recurrence of depression (Post, 1992; Mazure, 1998; Monroe and Harkness, 2005). Recurrent episodes, however, show less strong associations with stressful life events than

first onsets of depression do. This finding can be explained in two ways: 1. major life stress loses its *potential* to trigger depression (a progressive insensitivity to stress develops with recurrences of the disease, and alternative etiological mechanisms become increasingly important); 2. major life stress loses its *opportunity* to trigger depression (a progressive sensitivity to stress develops with recurrences of the disease, as a result of which increasingly minor stressors can provoke already a depressive episode) (see Monroe and Harkness, 2005). The latter explanation nicely fits in with stress-sensitization models of depression (e.g., Post and Weiss, 1998). The design of most studies, however, is unfit to distinguish between the two explanations (Monroe and Harkness, 2005; but see Brilman and Ormel, 2001; Ormel et al., 2001).

Although many depressed people have experienced a stressful life event before the onset of their depressive episode, only a minority of the people exposed to stressful life events become depressed. This observation has led to the supposition that there are individual differences in stress reactivity. Predispositional and contextual factors may modify the effects of a stressor, enhancing or diminishing its impact. Such thinking is the core of diathesis-stress models of depression, which propose that stress activates a diathesis (vulnerability), transforming a predisposition into the presence of psychopathology (Monroe and Simons, 1991). The negative cognitive schemas of Beck are a good example of such a diathesis, and neuroticism is also frequently conceived of in this way. Stress-buffering models of depression are the positive counterparts of diathesis-stress models. They assume that certain resilience factors protect the individual against depression by buffering the effects of stress. One important resilience factor is social support (Cohen and Wills, 1985; Coyne and Downey, 1991; Rhodes and Lakey, 1999).

3 INTERRELATIONSHIPS BETWEEN THE DIFFERENT RESEARCH FIELDS

Background idea of this thesis is that factors from different fields of depression research do not figure as isolated risk factors for depression but are related to each other. Such relationships can be causal, one factor leading to the other. In such a case, the one factor may mediate the effect of the other factor, the latter acting as a more proximate cause of depression (mediation). Factors can also act as modulators of one another, enhancing or reducing each other's effect (moderation). Another possibility is that factors are related to

each other because of a conceptual overlap, i.e. that they (partly) measure the same thing. Finally, factors can covary without further being related to each other, for example when they share a common cause.

The empirical literature provides some evidence for interrelationships between factors from the fields of our interest. In this section we review what is known. Where available, we also address relevant theories of depression that incorporate interfield relationships. The presented material serves as a basis for the multifactorial model of recurrence of depression that we will propose in section 4.2.

3.1 Personality ↔ social cognition

As becomes clear from influential definitions of neuroticism like the one of Costa and McCrae (see above), part of neuroticism reflects cognitive traits. Most researchers expect neuroticism to be related to the cognitive processing of emotional rather than neutral information (Martin, 1985). This is because neuroticism is generally conceived of as influencing a person's responsiveness to emotional stimuli. Indeed, several studies suggest that high neuroticism favors the cognitive processing of negative emotional information (Martin, 1985; Rusting, 1998). Mainly studies using memory tasks have found such relationships (Martin, 1985). Individuals high on neuroticism show enhanced recall of negative information, especially when the information is self-referent. Studies on the relationship between neuroticism and other aspects of cognitive processing, like attention, interpretation, or speed of perception, show less consistent results (Rusting, 1998). There is some evidence that individuals high on neuroticism show increased attention to negative or threatening information, that they are more likely to interpret stimuli in a negative way, and that they are faster to respond to negative stimuli (Rusting, 1998; Geerts and Bouhuys, 1998). Not all studies found such relationships, however, and in studies that did, it was often necessary to prime subjects prior to the cognitive assessment by means of stress- or mood induction (Mathews and MacLeod, 1994; Eysenck, 2000).

To summarize, part of neuroticism is conceived of as the tendency to process emotionally relevant information in a negative way. Empirical evidence is generally supportive of this conception, although the most convincing evidence comes from priming studies and studies using memory tasks.

3.2 Personality ↔ interpersonal behavior

Although behavior is often implicated in definitions of neuroticism and other personality traits (e.g., Costa and McCrae, 1987; Clark et al. 1994), personality research does not provide many data on what individuals actually do (Funder, 2001). This may have to do with the lack of consensus concerning what behaviors to measure and the time-consuming nature of behavioral observation studies. A number of studies have been done on the relationship between neuroticism and emotional expressiveness. These generally report a negative correlation, neurotics being less able to accurately express emotions (Riggio and Riggio, 2002). One study reports that neuroticism is related to gaze aversion (Campbell and Rushton, 1978). One study, in which a range of nonverbal behaviors was measured, found that neuroticism was related to an unfriendly expression and a soft and unpleasant voice (Borkenau and Liebler, 1995). Two other studies measuring a range of nonverbal behaviors did not find any significant correlations between neuroticism and behavior (Berry and Sherman-Hansen, 2000; Spain et al., 2000). In a study of our own research group, in which mutual adjustment of nonverbal involvement behavior was measured, no associations with neuroticism were found either (Geerts et al., 2000).

In sum, neuroticism is generally supposed to be reflected in (interpersonal) behavior, but evidence for this supposition is not abundant and results vary with the kind of behavior measured.

3.3 Personality ↔ stress physiology

Both high neuroticism and HPA-axis hyperactivity are considered as reflecting increased reactivity to stress. Therefore, one would expect a positive association between these two measures. Some studies indeed found such an association. High neuroticism has been related to high basal cortisol levels (Bridges and Jones, 1968) as well as to an increased cortisol response after a challenge (Houtman and Bakker, 1991; Kirschbaum et al., 1995; Zobel et al. 2004). One study, however, found a *de*creased cortisol response after a challenge in neurotic individuals (McCleery and Goodwin, 2001). In two other studies, neuroticism was not related to cortisol levels at all, neither at baseline nor after a challenge (Roy, 1996; Schommer et al., 1999). Another study found neuroticism to be related to plasma cortisol but not to urinary cortisol (Miller et al., 1999). Thus, studies on the association between neuroticism and HPA-axis hyperactivity have yielded mixed results so far.

3.4 Personality ↔ interpersonal stress

Whereas stress reactivity is considered a main element of neuroticism, neuroticism is probably also related to stress *exposure*. A number of studies found that individuals high on neuroticism are more likely to experience stressful life events than individuals low on neuroticism (Fergusson and Horwood, 1987; Headey and Wearing, 1989; Ormel and Wohlfarth, 1991; Poulton and Andrews, 1992; Magnus et al., 1993; Van Os et al., 2001; Kendler et al., 2003). Some other studies, however, failed to find such an association (Zautra et al., 1991; Ormel et al., 2001; Neeleman et al., 2003; Saudino et al., 1997 (elderly); Oldehinkel et al., 2003 (elderly)). The type of events that is investigated also makes a difference: "person-dependent" events (events that individuals may have brought upon themselves) seem to be more strongly associated with neuroticism than "person-independent" events (events that are "bad luck" or happen due to the actions of others) (Ormel, 1983; Ormel and Wohlfarth, 1991; Poulton and Andrews, 1992). Especially dependent events that involve interpersonal relationships are associated with neuroticism (Bolger and Schilling, 1991; Gunthert et al., 1999; Ormel et al., 2004c). It is not clear *why* high-neuroticism individuals seem to be more event prone. Many authors suggest that the reason must be found in the way neurotics behave or select their environment, but there is very little explicit research done to investigate this.

A number of studies report a modulating effect of neuroticism on stressful life events; individuals high on neuroticism seem to be more sensitive to the depressogenic effects of stressful events (Ormel et al., 1989; Bolger and Schilling, 1991; Gunthert et al., 1999; Van Os and Jones, 1999; Ormel et al., 2001; Kendler et al., 2004). These studies are in line with the common notion that neuroticism acts as a vulnerability factor in the etiology of depression; it is supposed to render the individual at risk of becoming depressed especially following adversity.

To conclude, evidence that neuroticism leads to a higher exposure to stressful life events is suggestive though not entirely consistent. Neuroticism probably (also) reflects a higher sensitivity to the effects of stressful events.

3.5 Stress physiology ↔ social cognition

The widespread use of synthetic analogues of cortisol in the treatment of inflammatory diseases (e.g., prednisone) has lead to the clinical observation that corticosteroids have also important (side-)effects on cognition. Empirical

studies have confirmed this observation. Elevated levels of corticosteroids generally are detrimental to cognitive functioning, especially when exposure is sustained (Lupien and McEwen, 1997; Sapolsky et al., 2000; Wolkowitz et al., 2001; Lupien et al., 2005). Mainly arousal, attention, and memory function are affected by persistent hypercortisolism.

In the short term, elevated cortisol levels serve to increase alertness and to focus attention, which is clearly adaptive under stressful circumstances (Wolkowitz et al., 2001; Erickson et al., 2003). Acute cortisol elevations also modulate the processing of emotional stimuli (Sapolsky et al., 2000; Lupien et al., 2005). In particular, the selective processing of threatening stimuli is enhanced (Rosen and Schulkin, 1998; Erickson et al., 2003). The relationship is reciprocal; the perception of threat also enhances cortisol excretion (as, for example, in the initiation of the stress response). Usually, feedback mechanisms serve to downregulate this system, preventing it from overshooting. Prolonged or repeated hypercortisolism, however, may induce long-lasting changes in this "fear circuit", so that an increased sensitivity to fearful or other negative stimuli may persist even while cortisol concentrations return to normal levels (Post and Weiss, 1998; Erickson et al., 2003; Bouhuys et al., 2005). In such a hyperexcitable fear circuit, elevated cortisol and threat perception have an excessive and prolonged effect upon each other, which is thought to play an important role in many forms of psychopathology (Rosen and Schulkin, 1998). Thus, with regard to the cognitive processing of emotional stimuli, cortisol and cognition mutually influence each other. In pathological cases these reciprocal effects become exaggerated and longer lasting.

3.6 Stress physiology ↔ interpersonal behavior

HPA-axis hyperactivity has been associated with a typical behavioral response to interpersonal stress characterized by submissiveness, inhibition, and social avoidance (Henry, 1982; Weinstock, 1997). Animal studies, for example, have shown that high cortisol levels are related to low social status and subordinate behavior in hierarchically organized species (Sapolsky, 1999; Abbott et al., 2003). Studies of humans have shown that high cortisol is related to shyness, social withdrawal, and fearful and internalizing behavior (Kagan et al., 1988; Granger et al., 1996; Legendre and Trudel, 1996; Gunnar et al., 1997; Schmidt et al., 1997; Fernald and Grantham-McGregor, 1998; Cacioppo et al., 2000; Goldsmith and Lemery, 2000; Smider et al., 2002). It is not clear which of the

two comes first, behavioral inhibition or hypercortisolism. The relationship is probably a complex one, allowing reciprocal influences, which may be modulated by early or severe stress (Henry, 1982; Kagan et al., 1988; Gunnar, 1994; Weinstock, 1997).

Typically, most of the above studies were done in children, and in all studies global qualitative measures were used to assess interpersonal behavior. We found 2 studies with quantitative measures of discrete nonverbal behaviors (Sgoifo et al., 2003; Makatsori et al., 2004), one of which confirms the idea that inhibitory behavior is related to higher HPA-axis activation, while the other seems to do not.

To summarize, high cortisol is related to inhibitory or fearful behavior, but the causal direction of this relationship is unclear. Studies relating cortisol to quantitative measures of nonverbal interpersonal behavior are uncommon.

3.7 Stress physiology ↔ interpersonal stress

The relationship between cortisol and interpersonal stress is a rather trivial one, since cortisol is conceptualized as a "stress hormone". It is released under stressful circumstances, thus likely also after interpersonal stress. The inverse relationship is not trivial; HPA-axis (hyper-)activity may contribute to the occurrence of interpersonal stress, or modulate its effects. There is a dearth of empirical studies in this respect. We found 3 studies that related HPA-axis hyperactivity to the subsequent occurrence of stressful life events, one of which indeed found such an association (Goodyer et al., 2001), the other two reporting a negative result (Charles et al., 1989; Harris et al., 2000). We did not find studies explicitly investigating modulatory effects of HPA-axis hyperactivity on stressful life events. Indirect evidence, however, suggests that such effects are likely. Individuals with a hyperactive HPA axis show an exaggerated, inappropriate, or prolonged response to stressful stimuli (Glue et al., 1993), and there is also evidence that these individuals exhibit less efficient coping strategies (Weinstock, 1997). So, the *impact* of a stressful life event presumably varies with the sensitivity of the physiological stress system.

3.8 Social cognition ↔ interpersonal stress

The main cognitive models of depression are diathesis-stress models; they postulate that cognitive factors act as a diathesis that increases risk of depression especially in combination with stressful events (cf. Abramson et al., 2002). Stressful events serve as triggers that activate negative cognitive

schemas (Beck, 1967) or negative attributional styles (Abramson et al., 1989), leading to the onset or exacerbation of depressive symptoms (Sweeney et al., 1986; Alloy et al., 1999). Cognitive factors may also influence the way in which stressful events are perceived or interpreted. For example, a cognitive bias toward threatening signals may make that stressors are more readily attended to or more easily interpreted as aversive (Gotlib and Hammen, 1992; Mineka and Gilboa, 1998). Further, the impact of a stressful event may vary with the individual's coping style (Cronkite and Moos, 1995; Nolen-Hoeksema, 2002). Avoidant and ruminative coping styles, for example, seem to increase the likelihood that stressful events become depressogenic, while active coping styles seem to reduce this likelihood. Differences in cognitive make-up may also make that different *types* of stressful events have a differential impact. Stressors that involve interpersonal relationships, for example, are supposed to be particularly depressogenic for individuals who are predominantly focused on interpersonal relationships (which are often women) (Champion and Power, 1995; Hammen, 1999; Nolen-Hoeksema, 2002). Individuals who are focused on other fields (e.g., achievement) are thought to be more sensitive to other types of stressors (e.g., work or financial stress).

The above theories and ideas suggest that (social) cognitions may interact with (interpersonal) stress, amplifying or reducing its effects, and there is some empirical evidence for all of them. A number of studies specifically investigated the interaction between stressful life events and the cognitive processing of emotional information. These studies showed that a processing bias toward threatening information predicts a stronger response to stressful life events (MacLeod and Hagan, 1992; Van den Hout et al., 1995; MacLeod et al., 2002; Pury, 2002; Beevers and Carver, 2003; Munafo and Stevenson, 2003).

The experience of stress may also affect emotion perception. There is evidence that stress has the potential to impair accurate decoding of emotional information (e.g., Gard et al., 1982; Keeley-Dyreson et al., 1991), and to enhance the selective processing of threat stimuli (Mogg et al., 1990; Mogg et al., 1994). These findings are consonant with those regarding the influence of elevated cortisol levels on cognition (see section 3.5), so cortisol is probably the more proximate factor here. We do not discuss this option further, as our design is unfit to test it; our stress measure (stressful life events) was assessed *after* our measure of emotion perception (cf. Box 1 at the end of this chapter). That is not to say that this option is not relevant (see also our remarks in section 4.2).

Some authors have raised the possibility that individuals may *generate* interpersonal stress as a result of their dysfunctional social cognitions (e.g., Hammen, 1999; Simons et al., 1993). For example, individuals who are not able to accurately decode the other's emotional expressions are probably less able to react appropriately to the other's signals, which may lead to interpersonal problems. Indirect evidence for this idea comes from a study that showed that individuals with low emotion decoding ability are experienced by others as less warm and sympathetic (Funder and Harris, 1986). Presumably, however, dysfunctional interpersonal behavior is an intermediating variable here; deficits in emotion perception likely first lead to inappropriate interpersonal behavior, which subsequently may lead to interpersonal problems (Gotlib and Hammen, 1992; Hammen, 1999, see below).

To conclude, several theories and empirical studies suggest that social cognitions can act as moderators of the effects of stressful life events, increasing or decreasing their impact. Social cognitions may also contribute to the occurrence of stressful life events, but presumably only indirectly, via behavior.

3.9 Interpersonal behavior ↔ interpersonal stress

The notion that some individuals may generate stressful life events as a result of their own behavior has received more and more attention in recent decades (e.g., Ormel, 1980; Ormel and Wohlfarth, 1991; Hammen, 1991; Potthoff et al., 1995). Hammen and colleagues, for example, showed in a number of longitudinal studies that depressed women were more likely than other groups to experience events of the dependent type (as opposed to events that occur independently of the individual's behavior) (Hammen, 1999). Especially dependent events that involved interpersonal relationships were elevated in these women. Importantly, these stress-generation patterns also occurred outside of periods of depression, were related to poor social problem-solving skills, and precipitated further depression.

The stress-generation theme is also an implicit element of the theories of Coyne and successors (cf. section 2.3). These propose that depressed and depression-prone individuals, because of their behavior, generate an array of interpersonal and other problems, which lead to onset, maintenance, or recurrence of depression (e.g., Coyne, 1976; Coyne et al., 1991; Segrin and Abramson, 1994; Coyne, 1999; Joiner, 2000; Joiner, 2002). The evidence for these ideas is suggestive, but mainly correlational in nature. Thus, depression,

dysfunctional interpersonal behavior, and interpersonal problems clearly covary, but evidence that dysfunctional behavior is also *antecedent* to interpersonal problems and subsequent depression is sparse (Marcus and Nardone, 1992; Segrin, 1998; Segrin, 2000; Joiner, 2000; Ormel et al., 2004a).

A few studies have prospectively linked interpersonal behavior to the occurrence of stressful life events (Potthoff et al., 1995; Davila et al., 1995; Segrin, 2001; Shahar et al., 2004). All but one (Segrin, 2001) found that dysfunctional interpersonal behavior or poor social skills indeed contribute to the occurrence of stressful life events. Interpersonal behavior was assessed by means of interviews or self-report questionnaires in these studies. There are no studies that relate observational measures of interpersonal behavior to the subsequent occurrence of stressful life events.

The opposite may also hold; the occurrence of stressful events likely also influences interpersonal behavior (e.g., Slane et al, 1980; Burgoon, 1985; Lehman et al., 1987; Pagano et al., 2004). We will not review the research on this topic, because the reverse relationship is more directly relevant to our case (stressful events being measured *after* the behavioral assessments; see Box 1).

In the tradition of diathesis-stress models of depression, some authors have proposed that dysfunctional interpersonal behavior might represent a diathesis for depression that increases risk only in combination with stressful events (e.g., Segrin and Flora, 2000). The reasoning behind this model is that people with good social skills can arrange sufficient social support, which buffers the effects of stressful events. Two studies (Frye and Goodman, 2000; Segrin and Flora, 2000), using self-report measures of social skills, provide some evidence for this suggestion. Another study, however, failed to find such a modulating effect of interpersonal behavior on stressful life events (Shahar et al., 2004). No studies with observational measures of interpersonal behavior are done on this topic.

In conclusion, although no studies with observational measures of non-verbal behavior exist that relate dysfunctional interpersonal behavior to the subsequent occurrence of stressful life events, such a relationship is plausible given existing theories and related empirical evidence.

3.10 Social cognition ↔ interpersonal behavior

Social cognition researchers for a long time focused on social cognition to the neglect of interpersonal behavior (Fiske, 1992). In recent decades, however, it

has become increasingly acknowledged that "social cognition is for social doing" (Fiske, 1992; Ostrom, 1994; Bandura, 2001). Concurrently, theories have begun to emerge that try to integrate cognitive and behavioral accounts of depression (e.g., Lewinsohn et al., 1985; Gotlib, 1992; Gotlib and Hammen, 1992; Patterson, 1995). In these theories also, cognitions are supposed to influence behavior. Activation of negative cognitive schemas, for example, is thought to lead to enhanced display of dysfunctional interpersonal behaviors (Lewinsohn et al., 1985; Gotlib and Hammen, 1992). Interpersonal behavior may also feed back on cognition according to these theories, but via the interpersonal consequences of that behavior (e.g., dysfunctional interpersonal behavior may induce aversion and rejection in others, the perception of which may reactivate negative cognitive schemas, *et cetera*; Lewinsohn et al., 1985; Gotlib and Hammen, 1992).

Empirical studies that relate social cognition to interpersonal behavior have become more frequent in recent decades as well, and the common notion in these studies also is that cognitions influence behavior. Focusing specifically on the relationship between the decoding of emotional expressions and interpersonal behavior, we found a number of studies done in children and schizophrenic patients (Penn et al., 1996; Most and Greenbank, 2000; Schultz et al., 2000; Hooker and Park, 2002). These studies report that lower decoding ability is related to poorer social functioning. Interpersonal behavior was assessed globally in these studies, by means of qualitative ratings of classroom or ward behavior by teachers or psychiatric nurses. Studies relating social cognition to quantitative measures of nonverbal behavior are rare. We found 3 studies. Dovidio et al. (2002) measured implicit racial prejudices using a cognitive priming task and related these to nonverbal and verbal friendliness behavior during interracial interactions. A cognitive racial bias appeared to go together with a similar bias in nonverbal friendliness, but not in verbal friendliness. Holland et al. (2004) investigated whether cognitive conceptualizations of the self (independent vs. interdependent self-concepts) influence interpersonal proximity in a waiting room. They found that a more independent self-concept was related to greater spatial distance between interactants. Geerts and Bouhuys (1998) investigated whether depressives' perception of negative emotions was related to the degree of mutual adjustment of nonverbal involvement behavior during a conversation, but found no such relationship.

To summarize, both theory and empirical evidence suggest that social

cognitions influence interpersonal behavior. Evidence based on studies using quantitative measures of nonverbal behavior is limited.

4 HYPOTHESES

On the basis of the literature reviewed above we have formulated the hypotheses that will be tested in the remainder of this thesis. We first present our hypotheses regarding the raw (univariate) relationships of the various factors to recurrence of depression, which are rather straightforward. Our hypotheses regarding the multivariate prediction of recurrence including factors from all 5 research fields are more explorative in nature.

4.1 Univariate prediction of recurrence

We expect that recurrence of depression can be predicted from:
1. Personality: high neuroticism
2. Social cognition: impaired emotion perception or a negative perceptual bias
3. Interpersonal behavior: poor nonverbal communication (lack of adjustment of nonverbal involvement behavior)
4. Stress physiology: HPA-axis hyperactivity (high cortisol levels)
5. Interpersonal stress: stressful life events (of the interpersonal type)

4.2 Interplay of putative determinants in the prediction of recurrence

Below, we do a proposal for a model on how the factors from the 5 different fields jointly may explain risk of recurrence of depression. The question of what neuroticism actually is and how it confers risk of depression is a leading issue here (see section 1). We are, however, also interested in the interplay as such of the various other factors in the prediction of recurrence. In our model, we show how neuroticism may be linked to recurrence by specifying intermediating and modulating effects of the factors from the other 4 fields. The literature regarding interfield relationships may not be always fully applicable to the present case (e.g., evidence often concerns healthy or depressed samples instead of remitted samples, interpersonal behavior is rarely assessed by direct observations of nonverbal behavior), it did give some direction to our thinking. Our proposal is based on what is most likely given this literature. In case there is plenty evidence from studies focusing on the specific factors of our interest, we relied on this evidence. In case there is not, we fell back on broader evidence and relevant theories.

Our model has certain constraints related to the study design (see Box 1). Stressful life events were assessed during the follow-up of our study, thus *after* the baseline measurements in which the other variables were assessed. Therefore, considering interpersonal stress or stressful life events as an *antecedent* of (changes in) the other variables is not suitable here. That means, we do not deny that stressful life events may have effects on the other variables, but we refrain from implementing such potential effects in our model as they are not testable within our design. For the same reason, we do not consider feedback loops in our model, although these are likely and should be included in a more complex model of depression which also includes long-term effects (cf. Gotlib and Hammen, 1992; Joiner, 2002).

The starting point of our model is neuroticism, this personality dimension so consistently associated with all kinds of distress and adversity while nobody knows for sure why. We expect that this elusive concept can be substantialized by measuring interpersonal behavior, social cognition, and stress physiology (see Figure 1). Specifically, we expect that high neuroticism becomes manifest in poor nonverbal communication, negative emotion perception, and HPA-axis hyperactivity (1). We suppose that each of these factors explains part of the risk of recurrence associated with neuroticism. Together, they may also explain why neurotic individuals are more prone to experience stressful life events, which further explains their increased risk of recurrence: We expect that HPA-axis hyperactivity and negative emotion perception mutually reinforce each other (2). Further, we expect that negative emotion perception leads to problems in nonverbal communication (3), and that problems in nonverbal communication contribute to the occurrence of stressful life events of the interpersonal type (4), which subsequently trigger depression. We also expect that some factors modulate the effect of other factors. Specifically, we expect that the effect of stressful interpersonal events is amplified by HPA-axis hyperactivity and negative emotion perception (5).

OUTLINE OF THE THESIS

Chapter 2 describes a pilot study on the prediction of depression relapse on the basis of interpersonal behavior. This study concerns a different sample than the one investigated in the rest of the thesis, and had a slightly different design. The sample consisted of inpatients who were just discharged from the

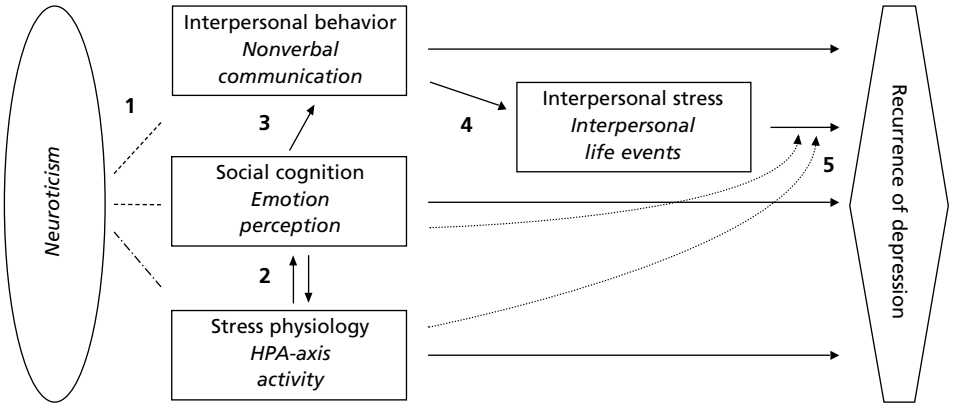


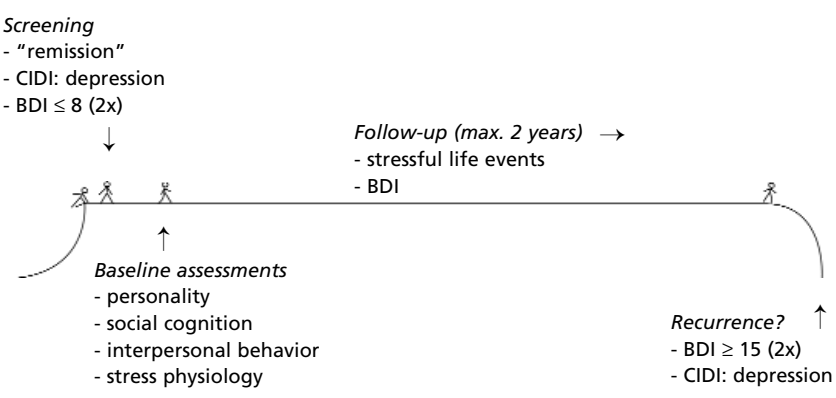
Figure 1 A multifactorial model of recurrence of depression. **1**. The personality dimension of neuroticism is reflected in poor nonverbal communication, negative emotion perception, and HPA-axis hyperactivity, each of which increases risk of depression. **2**. HPA-axis hyperactivity and negative emotion perception mutually reinforce each other. **3**. Negative emotion perception leads to poor nonverbal communication. **4**. Poor nonverbal communication contributes to the occurrence of stressful life events of the interpersonal type (which trigger depression). **5**. The effect of interpersonal events is amplified by negative emotion perception and HPA-axis hyperactivity.

hospital (n = 51). The follow-up was 6 months.

The Chapters 3 through 6 report on studies of a sample of remitted outpatients (n = 104), who were followed 2 years (see Box 1). *Chapter 3* investigates whether participants with a *history* of recurrent depression differ from participants with a single previous episode, as regards personality, social cognition, and stress physiology. *Chapter 4* deals with future recurrence, in particular with the question of whether it can be predicted from social cognition and stress physiology. *Chapter 5* describes a study on the prediction of recurrence from interpersonal behavior and personality. *Chapter 6* is also on the prediction of recurrence from interpersonal behavior, but now the question of whether stressful interpersonal events play an intermediating role in this relationship is investigated. In *Chapter 7* the findings are integrated and evaluated. This is done on the basis of the model that was presented above. In *Chapter 8* some implications for future research and clinical practice are discussed.

Box 1 Global study design

The study described in this thesis had a prospective longitudinal design with a 2-year follow-up. The determinants of interest were assessed at baseline, when the depression was in remission, and used to predict subsequent recurrence (see the figure below). Participants were outpatients recruited from mental health care centers in the northern part of the Netherlands, suffering from major depressive disorder or dysthymic disorder. They were asked to participate in the study if their psychiatrist considered them remitted from a depressive episode. We confirmed the psychiatrist's diagnosis by means of the Composite International Diagnostic Interview (CIDI, lifetime version; World Health Organization, 1997), a structured interview with good reliability and validity (Andrews and Peters, 1998). Remission was established by means of the Beck Depression Inventory (Beck and Steer, 1987), a widely used self-report depression scale with good psychometric properties (Beck et al., 1988). Participants were considered remitted in case the BDI score was 8 or less for 2 consecutive times, with a 4-week interval in between (following the consensus definition of Frank et al., 1991). Remitted participants (n = 104) underwent a series of baseline measurements on potential predictors of recurrence. These included self-report questionnaires to assess personality, computer tasks to assess social cognition (emotion perception), and videotaped interviews to assess interpersonal behavior (nonverbal communication). Stress physiology was assessed by measuring 24-h cortisol levels from urine samples that were collected the day after the baseline session. Stressful life events, which serve as a measure of (interpersonal) stress, were assessed over the whole length of the 2-year follow-up. Every 4 weeks during the follow-up, participants completed the BDI. They were suspected to have a recurrent episode if their BDI score was 15 or more for 2 consecutive times (cf. Frank et al., 1991). Recurrence was further established by means of the CIDI (12-months version).



REFERENCES

Abbott DH, Keverne EB, Bercovitch FB, Shively CA, Mendoza SP, Saltzman W, Snowdon CT, Ziegler TE, Banjevic M, Garland TJ, Sapolsky RM (2003) Are subordinates always stressed? A comparative analysis of rank differences in cortisol levels among primates. *Hormones and Behavior* 43, 67-82.

Abramson LY, Alloy LB, Hankin BL, Haeffel GJ, MacCoon DG, Gibb BE (2002) Cognitive vulnerability-stress models of depression in a self-regulatory and psychobiological context. In *Handbook of depression*, pp. 268-293. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Abramson LY, Metalsky GI, Alloy LB (1989) Hopelessness depression: A theory-based subtype of depression. *Psychological Review* 96, 358-372.

Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Tashman NA, Steinberg DL, Rose DT, Donovan P (1999) Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. *Behaviour Research and Therapy* 37, 503-531.

Andrews G, Peters L (1998) The psychometric properties of the Composite International Diagnostic Interview. *Social Psychiatry and Psychiatric Epidemiology* 33, 80-88.

Archer J, Hay DC, Young AW (1992) Face processing in psychiatric conditions. *British Journal of Clinical Psychology* 31, 45-61.

Austin MP, Mitchell P, Goodwin GM (2001) Cognitive deficits in depression: Possible implications for functional neuropathology. *British Journal of Psychiatry* 178, 200-206.

Bandura A (2001) Social cognitive theory: An agentic perspective. *Annual Review of Psychology* 52, 1-26.

Barnett PA, Gotlib IH (1988) Psychosocial functioning and depression: distinguishing among antecedents, concomitants, and consequences. *Psychological Bulletin* 104, 97-126.

Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ (2002) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder. *World Journal of Biological Psychiatry* 3, 5-43.

Bebbington P (1987) Misery and beyond: the pursuit of disease theories of depression. *International Journal of Social Psychiatry* 33, 13-20.

Beck AT (1967) *Depression: clinical, experimental, and theoretical aspects*. New York, NY: Hoeber.

Beck AT, Rush AJ, Shaw BF, Emery G (1985) *Cognitive therapy of depression*. New York, NY: Guilford Press.

Beck AT, Steer RA (1987) *Beck Depression Inventory; Manual*. New York, NY: Harcourt Brace & Company.

Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. *Clinical Psychology Review* 8, 77-100.

Beevers CG, Carver CS (2003) Attentional bias and mood persistence as prospective predictors of dysphoria. *Cognitive Therapy and Research* 27, 619-637.

Belsher G, Costello CG (1988) Relapse after recovery from unipolar depression: a critical review. *Psychological Bulletin* 104, 84-96.

Bernieri FJ, Rosenthal R (1991) Interpersonal coordination: Behavior matching and interactional synchrony. In *Fundamentals of nonverbal behavior*, pp. 401-432. Eds RS Feldman and B Rime. Cambridge: Cambridge University Press.

Berry DS, Sherman-Hansen J (2000) Personality, nonverbal behavior, and interaction quality in female dyads. *Personality and Social Psychology Bulletin* 26, 278-292.

Bolger N, Schilling EA (1991) Personality and the problems of everyday life: the role of neuroticism in exposure and reactivity to daily stressors. *Journal of Personality* 59, 355.

Borkenau P, Liebler A (1995) Observable attributes as manifestations and cues of personality and intelligence. *Journal of Personality* 63, 1-25.

Bouhuys AL, Geerts E, Gordijn MC (1999a) Gender-specific mechanisms associated with outcome of depression: perception of emotions, coping and interpersonal functioning. *Psychiatry Research* 85, 247-261.

Bouhuys AL, Geerts E, Gordijn MC (1999b) Depressed patients' perception of facial emotions in depressed and remitted state is associated with relapse: a longitudinal study. *Journal of Nervous and Mental Disease* 187, 595-602.

Bouhuys AL, Jansen CJ, Van den Hoofdakker RH (1991) Analysis of observed behavior displayed by depressed patients during a clinical interview: relationships between behavioral factors and clinical concepts of activation. *Journal of Affective Disorders* 21, 79-88.

Bouhuys AL, Oldehinkel AJ, Geerts E, Flentge F, Ormel J (2005) Cortisol and fear perception are associated but only in elderly depressed women. *Submitted*.

Bouhuys AL, Van den Hoofdakker RH (1993) A longitudinal study of interaction patterns of a psychiatrist and severely depressed patients based on observed behavior: an ethological approach of interpersonal theories of depression. *Journal of Affective Disorders* 27(2), 87-99.

Bridges PK, Jones MT (1968) Relationship of personality and physique to plasma cortisol levels in response to anxiety. *Journal of Neurology, Neurosurgery and Psychiatry* 31, 57-60.

Brilman EI, Ormel J (2001) Life events, difficulties and onset of depressive episodes in later life. *Psychological Medicine* 31, 859-869.

Brown GW (1993) The role of life events in the aetiology of depressive and anxiety disorders. In *Stress from synapse to syndrome*, pp. 23-50. Eds SC Stanford and P Salmon. London: Academic Press.

Brown GW, Harris T (1978) *Social origins of depression: a study of psychiatric disorder in women*. London: Tavistock.

Brown GW, Harris TO (1989) *Life events and illness*. New York, NY: Guilford Press.

Burgoon JK (1985) Nonverbal signals. In *Handbook of interpersonal communication*, pp. 344-390. Eds ML Knapp and GR Miller. Beverly Hills, CA: Sage Publications.

Burgoon JK, Dillman L, Stern LA (1993) Adaptation in dyadic interaction: defining and operationalizing patterns of reciprocity and compensation. *Communication Theory* 3, 295-316.

Cacioppo JT, Ernst JM, Burleson MH, McClintock MK, Malarkey WB, Hawkley LC, Kowalewski RB, Paulsen A, Hobson JA, Hugdahl K, Spiegel D, Berntson GG (2000) Lonely traits and concomitant physiological processes: the MacArthur social neuroscience studies. *International Journal of Psychophysiology* 35, 143-154.

Campbell A, Rushton JP (1978) Bodily communication and personality. *British Journal of Social and Clinical Psychology* 17, 31-36.

Cappella JN (1997) Behavioral and judged coordination in adult informal social interactions: Vocal and kinesic indicators. *Journal of Personality and Social Psychology* 72, 119-131.

Cappella JN, Palmer MT (1990) Attitude similarity, relational history, and attraction: The mediating effects of kinesic and vocal behaviors. *Communication Monographs* 57, 161-183.

Cappella JN (1996) Dynamic coordination of vocal and kinesic behavior in dyadic interaction: Methods, problems, and interpersonal outcomes. In *Dynamic patterns in communication processes*, pp. 353-386. Eds JH Watt and CA VanLear. Thousand Oaks, CA: Sage Publications.

Champion LA, Power MJ (1995) Social and cognitive approaches to depression: towards a new synthesis. *British Journal of Clinical Psychology* 34, 485-503.

Charles GA, Schittecatte M, Rush AJ, Panzer M, Wilmotte J (1989) Persistent cortisol non-suppression after clinical recovery predicts symptomatic relapse in unipolar depression. *Journal of Affective Disorders* 17, 271-278.

Chartrand TL, Bargh JA (1999) The chameleon effect: the perception-behavior link and social interaction. *Journal of Personality and Social Psychology* 76, 893-910.

Claridge G, Davis C (2001) What's the use of neuroticism? *Personality and Individual Differences* 31, 383-400.

Clark LA, Watson D, Mineka S (1994) Temperament, personality, and the mood and anxiety disorders. Special Issue: Personality and psychopathology. *Journal of Abnormal Psychology* 103, 103-116.

Cohen S, Wills TA (1985) Stress, social support, and the buffering hypothesis. *Psychological Bulletin* 98, 310-357.

Condon WS, Sander LW (1974) Synchrony demonstrated between movements of the neonate and adult speech. *Child Development* 45, 456-462.

Costa PT, McCrae RR (1987) Neuroticism, somatic complaints, and disease: Is the bark worse than the bite? *Journal of Personality* 55, 299-316.

Costello EJ, Pine DS, Hammen C, March JS, Plotsky PM, Weissman MM, Biederman J, Goldsmith HH, Kaufman J, Lewinsohn PM, Hellander M, Hoagwood K, Koretz DS, Nelson CA, Leckman JF (2002) Development and natural history of mood disorders. *Biological Psychiatry* 52, 529-542.

Cowen PJ (2002) Cortisol, serotonin and depression: all stressed out? *British Journal of Psychiatry* 180, 99-100.

Coyne JC (1976) Toward an interactional description of depression. *Psychiatry* 39, 28-40.

Coyne JC (1999) Thinking interactionally about depression: a radical restatement. In *The interactional nature of depression: advances in interpersonal approaches*, pp. 365-392. Eds TE Joiner and JC Coyne. Washington, DC: American Psychological Association.

Coyne JC, Burchill SAL, Stiles WB (1991) An interactional perspective on depression. In *Handbook of social and clinical psychology: The health perspective. Pergamon general psychology series, Vol. 162*, pp. 327-349. Eds CR Snyder and DR Forsyth. Elmsford, NY: Pergamon Press.

Cronkite RC, Moos RH (1995) Life context, coping processes, and depression. In *Handbook of depression (2nd ed.)*, pp. 569-586. Eds EE Beckham and WR Leber. New York, NY: Guilford Press.

Darwin C (1998) *The expression of the emotions in man and animals (1872)*. London: Harper Collins.

Davila J, Hammen C, Burge D, Paley B, Daley SE (1995) Poor interpersonal problem solving as a mechanism of stress generation in depression among adolescent women. *Journal of Abnormal Psychology* 104, 592-600.

Depaulo BM, Friedman HS (1998) Nonverbal communication. In *The handbook of social psychology, Vol. 2 (4th ed.)*, pp. 3-40. Eds DT Gilbert and ST Fiske. New York, NY: McGraw-Hill.

Dovidio JF, Kawakami K, Gaertner SL (2002) Implicit and explicit prejudice and interracial interaction. *Journal of Personality and Social Psychology* 82, 62-68.

Emerson CS, Harrison DW, Everhart DE (1999) Investigation of receptive affective prosodic ability in school-aged boys with and without depression. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 12, 102-109.

Enns MW, Cox BJ (1997) Personality dimensions and depression: review and commentary. *Canadian Journal of Psychiatry* 42, 274-284.

Erickson K, Drevets W, Schulkin J (2003) Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience and Biobehavioral Reviews* 27, 233-246.

Eysenck MW (2000) A cognitive approach to trait anxiety. *European Journal of Personality* 14, 463-476.

Feinberg TE, Rifkin A, Schaffer C, Walker E (1986) Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Archives of General Psychiatry* 43, 276-279.

Fergusson DM, Horwood LJ (1987) Vulnerability to life events exposure. *Psychological Medicine* 17, 739-749.

Fernald LC, Grantham-McGregor SM (1998) Stress response in school-age children who have been growth retarded since early childhood. *American Journal of Clinical Nutrition* 68, 691-698.

Fiske ST (1992) Thinking is for doing: portraits of social cognition from daguerreotype to laserphoto. *Journal of Personality and Social Psychology* 63, 877-889.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48, 851-855.

Frye AA, Goodman SH (2000) Which social problem-solving components buffer depression in adolescent girls? *Cognitive Therapy and Research* 24, 637.

Funder DC (2001) Personality. *Annual Review of Psychology* 52, 197-221.

Funder DC, Harris MJ (1986) On the several facets of personality assessment: The case of social acuity. *Journal of Personality* 54, 528.

Gaebel W, Wolwer W (1992) Facial expression and emotional face recognition in schizophrenia and depression. *European Archives of Psychiatry and Clinical Neuroscience* 242, 46-52.

Gard KA, Gard GC, Dossett D, Turone R (1982) Accuracy in nonverbal communication as affected by trait and state anxiety. *Perceptual and Motor Skills* 55, 747-753.

Geerts E, Bouhuys AL (1998) Multi-level prediction of short-term outcome of depression: the role of nonverbal interpersonal and cognitive processes and of personality traits. *Psychiatry Research* 79, 59-72.

Geerts E, Bouhuys AL, van den Hoofdakker RH (1996) Nonverbal attunement between depressed patients and an interviewer predicts subsequent improvement. *Journal of Affective Disorders* 40, 15-21.

Geerts E, Kouwert E, Bouhuys N, Meesters Y, Jansen J (2000) Nonverbal interpersonal attunement and extravert personality predict outcome of light treatment in seasonal affective disorder. *Journal of Affective Disorders* 59, 193-204.

Gilboa-Schechtman E, Erhard-Weiss D, Jeczemien P (2002) Interpersonal deficits meet cognitive biases: memory for facial expressions in depressed and anxious men and women. *Psychiatry Research* 113, 279-293.

Glue P, Nutt D, Coupland N (1993) Stress and psychiatric disorder: reconciling social and biological approaches. In *Stress. From synapse to syndrome*, pp. 53-72. Eds SC Stanford, P Salmon, and JA Gray. London: Harcourt Brace & Company.

Goldsmith HH, Lemery KS (2000) Linking temperamental fearfulness and anxiety symptoms: A behavior-genetic perspective. *Biological Psychiatry* 48, 1199-1209.

Goodyer IM, Park RJ, Herbert J (2001) Psychosocial and endocrine features of chronic first-episode major depression in 8-16 year olds. *Biological Psychiatry* 50, 351-357.

Gotlib IH (1992) Interpersonal and cognitive aspects of depression. *Current Directions in Psychological Science* 1, 149-154.

Gotlib IH, Hammen CL (1992) Toward a cognitive-interpersonal conceptualization of depression. In *Psychological aspects of depression; Toward a cognitive-interpersonal integration*, pp. 245-267. Chichester: John Whiley & Sons.

Gotlib IH, Krasnoperova E, Yue DN, Joormann J (2004) Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology* 113, 121-135.

Granger DA, Weisz JR, McCracken JT, Ikeda SC, Douglas P (1996) Reciprocal influences among adrenocortical activation, psychosocial processes, and the behavioral adjustment of clinic-referred children. *Child Development* 67, 3250-3262.

Gunnar MR, Tout K, de Haan M, Pierce S, Stansbury K (1997) Temperament, social competence, and adrenocortical activity in preschoolers. *Developmental Psychobiology* 31, 65-85.

Gunthert KC, Cohen LH, Armeli S (1999) The role of neuroticism in daily stress and coping. *Journal of Personality and Social Psychology* 77, 1087-1100.

Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg C, Kraemer HC (1992) Facial emotion discrimination: II. Behavioral findings in depression. *Psychiatry Research* 41, 241-251.

Gurguis GN, Meador-Woodruff JH, Haskett RF, Greden JF (1990) Multiplicity of depressive episodes: phenomenological and neuroendocrine correlates. *Biological Psychiatry* 27, 1156-1164.

Hale WH, Jansen JHC, Bouhuys AL (1998) The judgement of facial expressions by depressed patients, their partners and controls. *Journal of Affective Disorders* 47, 63-70.

Hammen C (1991) Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology* 100, 555-561.

Hammen C (1992) Cognitive, life stress, and interpersonal approaches to a developmental psychopathology model of depression. *Development and Psychopathology* 4, 189-206.

Hammen CL (1999) The emergence of an interpersonal approach to depression. In *The interactional nature of depression: Advances in interpersonal approaches*, pp. 21-35. Eds TE Joiner and JC Coyne. Washington, DC: American Psychological Association.

Harris TO, Borsanyi S, Messari S, Stanford K, Cleary SE, Shiers HM, Brown GW, Herbert J (2000) Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *British Journal of Psychiatry* 177, 505-510.

Headey B, Wearing A (1989) Personality, life events, and subjective well-being: Toward a dynamic equilibrium model. *Journal of Personality and Social Psychology* 57, 731-739.

Heim C, Nemeroff CB (2001) The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry* 49, 1023-1039.

Henry JP (1982) The relation of social to biological processes in disease. *Social Science and Medicine* 16, 369-380.

Higgins ET (1987) Self-discrepancy: a theory relating self and affect. *Psychological Review* 94, 319-340.

Holland RW, Roeder UR, van Baaren RB, Brandt AC, Hannover B (2004) Don't stand so close to me. The effects of self-construal on interpersonal closeness. *Psychological Science* 15, 237-242.

Holsboer F (2001) Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *Journal of Affective Disorders* 62, 77-91.

Hooker C, Park S (2002) Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Research* 112, 41-50.

Houtman IL, Bakker FC (1991) Individual differences in reactivity to and coping with the stress of lecturing. *Journal of Psychosomatic Research* 35, 11-24.

Isabella RA, Belsky J, Eye A (1989) Origins of mother-infant attachment: An examination of interactional synchrony during infant's first year. *Developmental Psychology* 25, 12-21.

Joiner TE (2000) Depression's vicious scree: Self-propagating and erosive processes in depression chronicity. *Clinical Psychology: Science and Practice* Vol 7, 203-218.

Joiner TE (2002) Depression and its interpersonal context. In *Handbook of depression*, pp. 295-313. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Joiner TE, Coyne JC (1999) *The interactional nature of depression: Advances in interpersonal approaches*. Washington, DC: American Psychological Association.

Just N, Abramson LY, Alloy LB (2001) Remitted depression studies as tests of the cognitive vulnerability hypotheses of depression onset: a critique and conceptual analysis. *Clinical Psychology Review* 21, 63-83.

Kagan J, Reznick JS, Snidman N (1988) Biological bases of childhood shyness. *Science* 240, 167-171.

Kaufman J, Plotsky PM, Nemeroff CB, Charney DS (2000) Effects of early adverse experiences on brain structure and function: clinical implications. *Biological Psychiatry* 48, 778-790.

Keeley-Dyreson M, Burgoon JK, Bailey W (1991) The effects of stress and gender on nonverbal decoding accuracy in kinesic and vocalic channels. *Human Communication Research* 17, 584-605.

Kendler KS, Kuhn J, Prescott CA (2004) The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry* 161, 631-636.

Kendler KS, Gardner CO, Prescott CA (2003) Personality and the experience of

environmental adversity. *Psychological Medicine* 33, 1193-1202.
Kendon A (1970) Movement coordination in social interaction: Some examples described. *Acta Psychologica* 32, 1-25.
Kessing LV, Hansen MG, Andersen PK, Angst J (2004) The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. *Acta Psychiatrica Scandinavica* 109, 339-344.
Kessler RC (1997) The effects of stressful life events on depression. *Annual Review of Psychology* 48, 191-214.
Kirschbaum C, Prussner JC, Stone AA, Federenko I, Gaab J, Lintz D, Schommer N, Hellhammer DH (1995) Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosomatic Medicine* 57, 468-474.
Klein DN, Durbin CE, Shankman SA, Santiago NJ (2002) Depression and personality. In *Handbook of depression*, pp. 115-140. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.
Lakin JL, Jefferis VE, Cheng CM, Chartrand TL (2003) The chameleon effect as social glue: Evidence for the evolutionary significance of nonconscious mimicry. *Journal of Nonverbal Behavior* 27, 145-162.
Legendre A, Trudel M (1996) Cortisol and behavioral responses of young children in a group of unfamiliar peers. *Merrill-Palmer Quarterly* 42, 554-577.
Lehman DR, Wortman CB, Williams AF (1987) Long-term effects of losing a spouse or child in a motor vehicle crash. *Journal of Personality and Social Psychology* 52, 218-231.
Leppanen JM, Milders M, Bell JS, Terriere E, Hietanen JK (2004) Depression biases the recognition of emotionally neutral faces. *Psychiatry Research* 128, 123-133.
Levkovitz Y, Lamy D, Ternochiano P, Treves I, Fennig S (2003) Perception of dyadic relationship and emotional states in patients with affective disorder. *Journal of Affective Disorders* 75, 19-28.
Lewinsohn PM, Hoberman HM, Teri L, Hautzinger M (1985) An integrative theory of depression. In *Theoretical issues in behavior therapy*, pp. 331-359. Eds S Reiss and RR Bootzin. New York, NY: Academic Press.
Luck P, Dowrick CF (2004) 'Don't look at me in that tone of voice!' Disturbances in the perception of emotion in facial expression and vocal intonation by depressed patients. *Primary Care Mental Health* 2, 99-106.
Lupien SJ, McEwen BS (1997) The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research and Brain Research Reviews* 24, 1-27.
Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, Tu MT (2005) Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology* 30, 225-242.
MacLeod C, Hagan R (1992) Individual differences in the selective processing of

threatening information, and emotional responses to a stressful life event. *Behaviour Research and Therapy* 30, 151-161.

MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L (2002) Selective attention and emotional vulnerability: Assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology* 111, 107-123.

Magnus K, Diener E, Fujita F, Pavot W (1993) Extraversion and neuroticism as predictors of objective life events: a longitudinal analysis. *Journal of Personality and Social Psychology* 65, 1046-1053.

Makatsori A, Duncko R, Moncek F, Loder I, Katina S, Jezova D (2004) Modulation of neuroendocrine response and non-verbal behavior during psychosocial stress in healthy volunteers by the glutamate release-inhibiting drug lamotrigine. *Neuroendocrinology* 79, 34-42.

Marcus DK, Nardone ME (1992) Depression and interpersonal rejection. *Clinical Psychology Review* 12, 433-449.

Marks MN, Wieck A, Checkley SA, Kumar R (1992) Contribution of psychological and social factors to psychotic and non-psychotic relapse after childbirth in women with previous histories of affective disorder. *Journal of Affective Disorders* 24, 253-263.

Martin M (1985) Neuroticism as predisposition toward depression: a cognitive mechanism. *Personality and Individual Differences* 6, 353-365.

Mathews A, MacLeod C (1994) Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology* 45, 25-50.

Mazure CM (1998) Life stressors as risk factors in depression. *Clinical Psychology: Science and Practice* 5, 291-313.

McCleery JM, Goodwin GM (2001) High and low neuroticism predict different cortisol responses to the combined dexamethasone/CRH test. *Biological Psychiatry* 49, 410-415.

McCrae RR, Costa PT (1999) A five-factor theory of personality. In *Handbook of personality: Theory and research*, pp. 139-153. Eds LA Pervin and OP John. New York, NY: Guilford Press.

McEwen BS (2000) Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology* 22, 108-124.

Meyer SE, Chrousos GP, Gold PW (2001) Major depression and the stress system: a life span perspective. *Developmental Psychopathology* 13, 565-580.

Mikhailova ES, Vladimirova TV, Iznak AF, Tsusulkovskaya EJ, Sushko NV (1996) Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. *Biological Psychiatry* 40, 697-705.

Miller GE, Cohen S, Rabin BS, Skoner DP, Doyle WJ (1999) Personality and tonic cardiovascular, neuroendocrine, and immune parameters. *Brain, Behavior, and Immunity* 13, 109-123.

Mineka S, Gilboa E (1998) Cognitive biases in anxiety and depression. In *Emotions in psychopathology: Theory and research. Series in affective science*, pp. 216-228. Eds WFJ Flack and JD Laird. London: Oxford University Press.

Miranda J, Gross JJ (1997) Cognitive vulnerability, depression, and the mood-state dependent hypothesis: Is out of sight out of mind? *Cognition and Emotion* 11, 585-605.

Mogg K, Bradley BP, Hallowell N (1994) Attentional bias to threat: roles of trait anxiety, stressful events, and awareness. *Quarterly Journal of Experimental Psychology (A)* 47, 841-864.

Mogg K, Mathews A, Bird C, Macgregor-Morris R (1990) Effects of stress and anxiety on the processing of threat stimuli. *Journal of Personality and Social Psychology* 59, 1230-1237.

Monroe SM, Simons AD (1991) Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychological Bulletin* 110, 406-425.

Monroe SM, Harkness KL (2005) Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychological Review* 112, 417-445.

Most T, Greenbank A (2000) Auditory, visual, and auditory-visual perception of emotions by adolescents with and without learning disabilities, and their relationship to social skills. *Learning Disabilities Research and Practice* 15, 171-178.

Munafo MR, Stevenson J (2003) Selective processing of threat-related cues in day surgery patients and prediction of post-operative pain. *British Journal of Health Psychology* 8, 439-449.

Murphy D, Cutting J (1990) Prosodic comprehension and expression in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry* 53, 727-730.

Neeleman J, Bijl R, Ormel J (2004) Neuroticism, a central link between somatic and psychiatric morbidity: path analysis of prospective data. *Psychological Medicine* 34, 521-531.

Neeleman J, Oldehinkel AJ, Ormel J (2003) Positive life change and remission of non-psychotic mental illness. A competing outcomes approach. *Journal of Affective Disorders* 76, 69-78.

Neeleman J, Sytema S, Wadsworth M (2002) Propensity to psychiatric and somatic ill-health: evidence from a birth cohort. *Psychological Medicine* 32, 793-803.

Nolen-Hoeksema S (2002) Gender differences in depression. In *Handbook of depression*, pp. 492-509. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Oldehinkel AJ, Ormel J, Brillman EI (2003) Personality does not predict stressful event occurrence in elderly persons. *Social Behavior and Personality* 31(1), 49-54.

Ormel J (1980) *Moeite met leven of een moeilijk leven (Problems with life or a stressful life)*. Groningen: Konstapel.

Ormel J (1983) Neuroticism and well-being inventories: measuring traits or states?

Psychological Medicine 13, 165-176.
Ormel J, Oldehinkel AJ, Brilman EI (2001) The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry* 158, 885-891.
Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W (2004a) Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. *Archives of General Psychiatry* 61, 387-392.
Ormel J, Oldehinkel AJ, Vollebergh W (2004b) Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Archives of General Psychiatry* 61, 990-996.
Ormel J, Stewart R, Sanderman R (1989) Personality as modifier of the life change-distress relationship. A longitudinal modelling approach. *Social Psychiatry and Psychiatric Epidemiology* 24, 187-195.
Ormel J, Rosmalen J, Farmer A (2004c) Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* 39, 906-912.
Ormel J, Wohlfarth T (1991) How neuroticism, long-term difficulties, and life situation change influence psychological distress: a longitudinal model. *Journal of Personality and Social Psychology* 60(5), 744-755.
Ostrom TM (1994) Foreword. In *Handbook of social cognition, Vol. 1: Basic processes*, pp. vii-xii. Eds RSJr Wyer and TK Srull. Hillsdale, NJ: Lawrence Erlbaum Associates.
Pagano ME, Skodol AE, Stout RL, Shea MT, Yen S, Grilo CM, Sanislow CA, Bender DS, McGlashan TH, Zanarini MC, Gunderson JG (2004) Stressful life events as predictors of functioning: findings from the Collaborative Longitudinal Personality Disorders Study. *Acta Psychiatrica Scandinavica* 110, 421-429.
Patterson ML (1995) Invited article: A parallel process model of nonverbal communication. *Journal of Nonverbal Behavior* 19, 3-29.
Paykel ES (1994) Life events, social support and depression. *Acta Psychiatrica Scandinavica* 89, 50-58.
Paykel ES (2003) Life events and affective disorders. *Acta Psychiatrica Scandinavica* Supplement 61-66.
Penn DL, Spaulding W, Reed D, Sullivan M (1996) The relationship of social cognition to ward behavior in chronic schizophrenia. *Schizophrenia Research* 20, 327-335.
Persad SM, Polivy J (1993) Differences between depressed and nondepressed individuals in the recognition of and response to facial emotional cues. *Journal of Abnormal Psychology* 102, 358-368.
Persons JB, Miranda J (1992) Cognitive theories of vulnerability to depression: reconciling negative evidence. *Cognitive Therapy and Research* 16, 485-502.
Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent

affective disorder. *American Journal of Psychiatry* 149, 999-1010.
Post RM, Weiss SRB (1998) Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness progression. *Biological Psychiatry* 44, 193-206.
Potthoff JG, Holahan CJ, Joiner T-EJ (1995) Reassurance seeking, stress generation, and depressive symptoms: an integrative model. *Journal of Personality and Social Psychology* 68, 664-670.
Poulton RG, Andrews G (1992) Personality as a cause of adverse life events. *Acta Psychiatrica Scandinavica* 85, 35-38.
Pury CLS (2002) Information-processing predictors of emotional response to stress. *Cognition and Emotion* 16, 667-683.
Rhodes GL, Lakey B (1999) Social support and psychological disorder: Insights from social psychology. In *The social psychology of emotional and behavioral problems: Interfaces of social and clinical psychology*, pp. 281-309. Eds RM Kowalski and MR Leary. Washington, DC: American Psychological Association.
Ribeiro SC, Tandon R, Grunhaus L, Greden JF (1993) The DST as a predictor of outcome in depression: A meta-analysis. *American Journal of Psychiatry* 150, 1618-1629.
Ridout N, Astell AJ, Reid IC, Glen T, O'Carroll RE (2003) Memory bias for emotional facial expressions in major depression. *Cognition and Emotion* 17, 101-122.
Rosen JB, Schulkin J (1998) From normal fear to pathological anxiety. *Psychological Review* 105, 325-350.
Roy A (1996) HPA axis function and temperament in depression: a negative report. *Biological Psychiatry* 39, 364-366.
Rude SS, Wenzlaff RM, Gibbs B, Vane J, Whitney T (2002) Negative processing biases predict subsequent depressive symptoms. *Cognition and Emotion* 16, 423-440.
Rusting CL (1998) Personality, mood, and cognitive processing of emotional information: Three conceptual frameworks. *Psychological Bulletin* 124, 165-196.
Sapolsky RM (1999) Hormonal correlates of personality and social contexts: From non-human to human primates. In *Hormones, health, and behavior: A socio-ecological and lifespan perspective*, pp. 18-46. Eds C Panter-Brick and CM Worthman. Cambridge: Cambridge University Press.
Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews* 21, 55-89.
Saudino KJ, Pedersen NL, Lichtenstein P, McClearn GE, Plomin R (1997) Can personality explain genetic influences on life events? *Journal of Personality and Social Psychology* 72, 196-206.
Schmidt LA, Fox NA, Rubin KH, Sternberg EM (1997) Behavioral and neuroendocrine responses in shy children. *Developmental Psychobiology* 30, 127-140.
Schommer NC, Kudielka BM, Hellhammer DH, Kirschbaum C (1999) No evidence for a

close relationship between personality traits and circadian cortisol rhythm or a single cortisol stress response. *Psychological Reports* 84, 840-842.

Schultz D, Izard C, Ackerman BP (2000) Children's anger attribution bias: relations to family environment and social adjustment. *Social Development* 9, 284-301.

Segal ZV, Ingram RE (1994) Mood priming and construct activation in tests of cognitive vulnerability to unipolar depression. *Clinical Psychology Review* 14, 663-695.

Segrin C (2000) Social skills deficits associated with depression. *Clinical Psychology Review* 20, 379-403.

Segrin C, Abramson LY (1994) Negative reactions to depressive behaviors: a communication theories analysis. *Journal of Abnormal Psychology* 103(4), 655-668.

Segrin C (2001) Social skills and negative life events: Testing the deficit stress generation hypothesis. *Current Psychology* 20, 19-35.

Segrin C (1998) Interpersonal communication problems associated with depression and loneliness. In *Handbook of communication and emotion; Research, theory, applications, and contexts*, pp. 215-242. Eds PA Anderson and LK Guerrero. San Diego: Academic Press.

Segrin C, Flora J (2000) Poor social skills are a vulnerability factor in the development of psychosocial problems. *Human Communication Research* 26, 489-514.

Sgoifo A, Braglia F, Costoli T, Musso E, Meerlo P, Ceresini G, Troisi A (2003) Cardiac autonomic reactivity and salivary cortisol in men and women exposed to social stressors: Relationship with individual ethological profile. *Neuroscience and Biobehavioral Reviews* 27, 179-188.

Shahar G, Joiner J, Zuroff DC, Blatt SJ (2004) Personality, interpersonal behavior, and depression: co-existence of stress-specific moderating and mediating effects. *Personality and Individual Differences* 36, 1583-1596.

Simons AD, Angell KL, Monroe SM, Thase ME (1993) Cognition and life stress in depression: cognitive factors and the definition, rating, and generation of negative life events. *Journal of Abnormal Psychology* 102, 584-591.

Slane S, Dragan W, Crandall CJ, Payne P (1980) Stress effects on the nonverbal behavior of repressors and sensitizers. *Journal of Psychology* 106, 101-109.

Smider NA, Essex MJ, Kalin NH, Buss KA, Klein MH, Davidson RJ, Goldsmith HH (2002) Salivary cortisol as a predictor of socioemotional adjustment during kindergarten: a prospective study. *Child Development* 73, 75-92.

Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, Coryell W, Warshaw M, Turvey C, Maser JD, Endicott J (2000) Multiple recurrences of major depressive disorder. *American Journal of Psychiatry* 157, 229-233.

Spain JS, Eaton LG, Funder DC (2000) Perspectives on personality: the relative accuracy of self versus others for the prediction of emotion and behavior. *Journal of Personality* 68, 837-867.

Strickland PL, Deakin JF, Percival C, Dixon J, Gater RA, Goldberg DP (2002) Bio-social

origins of depression in the community. Interactions between social adversity, cortisol and serotonin neurotransmission. *British Journal of Psychiatry* 180, 168-173.

Surguladze SA, Young AW, Senior C, Brebion G, Travis MJ, Phillips ML (2004) Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology* 18, 212-218.

Surtees PG, Wainwright NW (1996) Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. *British Journal of Psychiatry* 169, 338-347.

Sweeney PD, Anderson K, Bailey S (1986) Attributional style in depression: A meta-analytic review. *Journal of Personality and Social Psychology* 50, 974-991.

Teasdale JD (1988) Cognitive vulnerability to persistent depression. *Cognition and Emotion* 2, 247-274.

Thase ME, Jindal R, Howland RH (2002) Biological aspects of depression. In *Handbook of Depression*, pp. 192-218. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Thase ME, Howland RH (1995) Biological processes in depression: An updated review and integration. In *Handbook of depression (2nd ed.)*, pp. 213-279. Eds EE Beckham and WR Leber. New York, NY: Guilford Press.

Tickle-Degnen L, Rosenthal R (1990) The nature of rapport and its nonverbal correlates. *Psychological Inquiry* 1, 285-293.

Troisi AT, Pasini A, Bersani G, Grispini A, Ciani N (1989) Ethological predictors of amitryptiline response in depressed outpatients. *Journal of Affective Disorders* 17, 129-136.

Van den Hout M, Tenney N, Huygens K, Merckelbach H, Kindt M (1995) Responding to subliminal threat cues is related to trait anxiety and emotional vulnerability: a successful replication of Macleod and Hagan (1992). *Behaviour Research and Therapy* 33, 451-454.

Van Os J, Jones PB (1999) Early risk factors and adult person-environment relationships in affective disorder. *Psychological Medicine* 29, 1055-1067.

Van Os J, Park SB, Jones PB (2001) Neuroticism, life events and mental health: evidence for person-environment correlation. *British Journal of Psychiatry Supplement* 40, 72-77.

Walker E, McGuire M, Bettes B (1984) Recognition and identification of facial stimuli by schizophrenics and patients with affective disorders. *British Journal of Clinical Psychology* 23, 37-44.

Weary G, Edwards JA (1994) Social cognition and clinical psychology: Anxiety, depression, and the processing of social information. In *Handbook of social cognition, Vol. 2: Applications*, pp. 289-338. Eds RSJr Wyer and TK Srull. Hillsdale, NJ: Lawrence Erlbaum Associates.

Weinstock M (1997) Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neuroscience and Biobehavioral Reviews* 21, 1-10.

Williams JMG, Watts FN, MacLeod C, Mathews A (1997) *Cognitive psychology and emotional disorders*. Chichester: Wiley.

Wolkowitz OM, Epel ES, Reus VI (2001) Stress hormone-related psychopathology: pathophysiological and treatment implications. *World Journal of Biological Psychiatry* 2, 115-143.

World Health Organization (1997) *Composite International Diagnostic Interview (CIDI), version 2.1. Dutch translation and revision*. Amsterdam: AMC.

Zautra AJ, Finch JF, Reich JW, Guarnaccia CA (1991) Predicting the everyday life events of older adults. *Journal of Personality* 59, 507-538.

Zobel A, Barkow K, Schulze-Rauschenbach S, Von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W (2004) High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatrica Scandinavica* 109, 392-399.

Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001) Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. *Journal of Psychiatric Research* 35, 83-94.

Zobel AW, Yassouridis A, Frieboes RM, Holsboer F (1999) Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. *American Journal of Psychiatry* 156, 949-951.

Zuroff DC, Colussy SA (1986) Emotion recognition in schizophrenic and depressed patients. *Journal of Clinical Psychology* 42(3), 411-416.

2

Nonverbal interaction involvement as an indicator of prognosis in remitted depressed subjects

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ABSTRACT

Fifty-one remitted depressed inpatients and their interviewers were observed during a conversation. We investigated whether nonverbal behavioral elements indicative of involvement displayed by the remitted patients and/or their interviewers were predictive of depressive symptoms 6 months later. Involvement behavior of the patients appeared to be related to future complaints; the lower the level of involvement displayed, the more unfavorable the outcome. We interpret these results with reference to concepts of social support.

INTRODUCTION

Depression is frequently associated with interpersonal dysfunctioning. Several theories have been formulated linking interpersonal factors to depressive disorder (Lewinsohn, 1974; Coyne, 1976; Coyne et al., 1991; Gotlib and Hammen, 1992). Social support and well-developed social networks are supposed to protect against depression, to facilitate recovery, and to prevent recurrence. Problems in interpersonal functioning and lack of social competence are thought to lead to interpersonal stress and withdrawal of the social environment and, via these, to increase risk of depression.

This credible idea of a link between depression and the interpersonal is supported by a considerable amount of empirical research. Several studies show that depressives have problems in social functioning, and that these problems are associated with poor recovery and chronicity of the depression (see Lara and Klein, 1999; Joiner, 2000). Most of these studies, however, merely tell us something about interpersonal problems of individuals while they *are* depressed and about how these problems relate to episode duration. Little is known about social functioning of nondepressed or recovered individuals and its implications for depression onset and recurrence. Evidence at all that interpersonal factors are predictive of the development of depressive disorders and of relapse or recurrence is scarce (Paykel, 1994; Joiner, 2000).

It is not unreasonable to hypothesize that the factors responsible for interpersonal problems in depressed patients are also the ones that make individuals vulnerable for development and recurrence of depression. Such would be consistent with the diathesis-stress model of depression, which presumes that certain underlying traits (that interact with stressful events) predispose people to depression (e.g., Bebbington, 1987; Perris, 1987; Robins and Block, 1989). Reasoning within the lines of this model, one would expect interpersonal problems not to be confined to the depressive state, but to endure in remission, reflecting an underlying vulnerability. Some longitudinal studies with measurements both in depression and in remission support this idea. Marital discord and lack of close relationships have been shown to continue when the depression is over, and to predict relapse and recurrence (e.g., Rounsaville et al., 1980; Billings and Moos, 1985a; Billings and Moos, 1985b). Other studies, however, could not establish that the social factors that impede recovery in depressed patients are also the ones that increase risk of

recurrence in recovered patients (see Barnett and Gotlib, 1988). Anyhow, too few longitudinal studies focusing on interpersonal functioning of remitted or recovered patients have been done so far to be decisive upon this.

In the present study, we examine interpersonal interactions of inpatients while the depression is in remission. We want to investigate whether there is anything observable in the behavior of remitted patients and/or their conversation partners that differentiates individuals at high risk for relapse from others. Nonverbal, observable, behavior is an important, but often neglected aspect of interpersonal communication (cf. Burgoon, 1985; Cahn and Frey, 1992). Several nonverbal aspects of the behavior of depressives have been related to problems in social functioning (see Segrin, 1998). This appears to hold especially for nonverbal correlates of interaction involvement. Adequate levels of involvement behavior seem to be indispensable for the establishment and maintenance of satisfactory interpersonal relationships (cf. Cegala et al., 1982; Bell, 1987; Coker and Burgoon, 1987; Segrin and Abramson, 1994). Individuals showing very low levels of involvement behavior, for example, are easily experienced as unresponsive, unconcerned, and lacking initiative (e.g., Davis and Holtgraves, 1984; Burgoon et al., 1989). On the other hand, very high levels of involvement are likely experienced as a sign of dependency and excessive reassurance seeking (e.g., Harlow and Cantor, 1994). In either case, the reaction of the social environment may be aversion and rejection. Displaying adequate involvement in interactions thus seems to be a matter of a good balance.

In line with this, both extremes in involvement behavior of depressives have been related to unfavorable depression outcome. High levels of involvement (Troisi et al., 1989; Bouhuys and Albersnagel, 1992; Geerts et al., 1995), as well as low levels (Zeiss and Lewinsohn, 1988) have been found to be associated with poor recovery. These findings do not settle the question of how involvement behavior relates to depression. The way involvement was operationalized varied in these studies. Moreover, the association between involvement behavior and outcome was not consistently found. For instance, Hale et al. (1997b) could not find such an association. Geerts et al. (2000) did find a relationship between involvement and outcome, but only with regard to the behavior of the conversation partners of the depressives. Most importantly, the above studies again concern the behavior of depressed patients and its consequences for episode duration. Evidence that the same applies to the behavior of remitted patients having implications for depression relapse is

lacking. Hale et al. (1997a) did study involvement behavior in remitted patients, but in too small a sample to draw any firm conclusions (n = 34).

The present study is an extension of the above-mentioned study by Hale et al. (1997a). In a larger sample, we investigate nonverbal involvement behavior of remitted patients in a dyadic interaction. The behavior of the participants' interviewers and the interplay between participants and interviewers will be studied as well, since these may also contain prognostic information. Possibly, the interaction partners influence each others' displayed level of involvement, and the degree to which this happens may relate to depression outcome. Such "interviewer" and "interaction effects" were found in previous studies of our research group (Bouhuys and Van den Hoofdakker, 1993; Geerts et al., 1995; Geerts et al., 1996; Geerts et al., 1997; Geerts and Bouhuys, 1998; Geerts et al., 2000).

The behavioral elements we focus on in this study are gesticulations, head movements, gaze, verbal backchannel (i.e. small supportive sounds like "hm, hm" and "yes, yes" emitted during listening), and speech. These behaviors are considered to be indicative of involvement (see Cappella, 1983; Patterson, 1983; Coker and Burgoon, 1987; Bouhuys et al., 1991; Bouhuys and Van den Hoofdakker, 1991). We hypothesize that involvement as reflected in these behaviors is related to severity of depressive symptoms at 6 months after remission. As we do not know whether this relationship is a negative or a positive one, we will test our hypothesis bilaterally.

METHODS

Participants and design

We studied 51 inpatients recovered from a depressive episode (major depressive disorder, n = 41; dysthymic disorder, n = 1; and bipolar disorder (depressed phase), n = 9; with psychotic features, n = 25 (DSM-IV; American Psychiatric Association, 1994). The diagnosis was made at hospital admission by experienced psychiatrists. We assessed severity of depression by means of the Hamilton Rating Scale for Depression (HRSD, 21-item version; mean of two independent raters; Hamilton, 1967). This HRSD interview was done thrice: at hospital admission (T0), at remission (T1), and 6 months after remission (T2). The interviews were conducted between 9:00 AM and 12:00 AM. Interviewers were six researchers, three male and three female, with a mean age of 36.8

years (SD = 10.8; range 25–50). Patients were included in the present study if their HRSD score was at least 16 at admission and at most 8 at remission. All subjects gave their written informed consent to participate. The group consisted of 35 women and 16 men. Mean age at hospital admission was 46.6 (SD = 13.1, range 18–71). Average length of hospital stay was 141.7 days (SD = 70.6, range 48–323). At T0, mean group HRSD score was 24.1 (SD = 5.8, range 16–38). At T1, mean HRSD score was 4.3 (SD = 2.3, range 0.5–8.0). All participants received treatment according to their clinical needs. Most participants used psychotropic medication at remission: antidepressants, benzodiazepines, neuroleptics, antiparkinson treatment, lithium, or combinations of these.

Analysis of behavior

HRSD remission interviews were videotaped for later analysis of nonverbal behavior. The first 15 minutes of the videotaped interview were analyzed. Seven trained scorers registered various behavioral elements of the participant and the interviewer by means of an event-recording system. The mean interrater reliability (kappa; Cohen, 1968) was 0.89 (range 0.68–0.98). Different categories of behavioral elements were recorded in different runs of the videotape. Durations as well as frequencies of behaviors were registered. The behaviors were analyzed relative to a subject's speaking or listening, as the occurrence of these behaviors depends on whether one is doing one of the two.

We recorded different sets of behavioral elements for participants versus interviewers. With respect to the participant, we registered gesticulations (all sorts), general head movements, gaze, and speech. With respect to the interviewer, we measured yes-nodding, verbal backchannel, and speech. The choice of these specific sets of behavioral elements was based on a factor analytic study of participant and interviewer behavior done earlier by Bouhuys et al. (Bouhuys et al., 1991; Bouhuys and Van den Hoofdakker, 1991; Geerts et al., 1995). The difference in the collections of behaviors for participant vs. interviewer is a result of the outcome of this factor analysis. This outcome can be seen as a reflection of the different roles interviewers and interviewees have in a conversation, interviewers mainly listening and inquiring, interviewees mainly answering and telling. These two sets of behavioral elements proved to have predictive qualities in several studies of our group (Bouhuys and Albersnagel, 1992; Bouhuys and Van den Hoofdakker, 1993; Geerts et al., 1995; Geerts et al., 1996; Geerts and Bouhuys, 1998; Geerts et al., 2000).

Moreover, the two sets appeared to be (causally) related to one another (Bouhuys and Van den Hoofdakker, 1991; Geerts et al., 1997). In addition, in other studies these behavioral elements are also considered as indicative of involvement (e.g., Cappella, 1983; Patterson, 1983; Coker and Burgoon, 1987). For these reasons, we chose to hold on to them in the present study.

The behavior scores were normalized over the interviews, to enable pooling of the behavioral elements into two behavioral factors: "participant involvement" and "interviewer involvement". The factor "participant involvement" consisted of duration and frequency of gesticulations, duration and frequency of head movements, duration and frequency of gaze (all during speech), and duration of gaze during listening. This factor can be seen as a reflection of the amount of effort one puts in speaking (the factor has also been called "speaking effort"). The factor "interviewer involvement" consisted of duration and frequency of verbal backchannel and duration and frequency of yes-nodding (all during listening). This factor is considered to reflect the degree one is stimulating the other in speaking by showing one is attending and understanding (the factor has also been called "encouragement") (for a detailed description of the composition of the factors, see Geerts et al., 1995).

Statistical analysis

We employed partial correlation and linear multiple regression techniques to detect relationships between behavioral predictor variables measured in remission and depressive symptom scores 6 months later. In all equations with higher-order terms we used centered versions of first-order terms (Aiken and West, 1991). The upper level of significance to reject H_0 was set at 0.05.

RESULTS

Sample characteristics

At T2, 6 months after remission, mean HRSD score of the sample was 6.9 (SD = 6.6, range 0.5–30.5). The depression score of 37 of the 51 remitted patients had remained below the initial remission criterion of 8. The HRSD score of 10 participants had considerably increased at T2. These 10 participants could be labeled "relapsed" according to common criteria (HRSD score $\geq$ 12 and 100% increased relative to score at remission). Four participants had an intermediate

HRSD score (between 8 and 12). The thus distinguished subgroups are presented here only to describe the sample, and will not be used in further analyses.

HRSD remission scores (T1) appeared to be positively related to HRSD scores at T2 (Pearson's r = 0.30, p = .035). The amount of change in depression score from T1 to T2 was not related to age, length of antecedent hospitalization, or severity of depression at admission (partial correlations, correction for HRSD score at T1). Neither was change in depression score related to subtype of depression (unipolar or bipolar, with or without psychotic features; ANCOVA, correction for HRSD score at T1). Women, however, showed a higher increase in depression score than men (ANCOVA, correction for HRSD score at T1; $F(1,48) = 4.35$, $p = .042$). This gender difference is in line with the general higher risk of depression in women relative to men (Weissman and Klerman, 1977; Paykel, 1991). Baseline HRSD score (T1) was not different for the two sexes.

Male and female interviewers were evenly distributed over interviews with male and female participants (Chi-square test). No difference in change in depression score was found between participants with an interviewer of the same sex and participants with an interviewer of the opposite sex (ANCOVA, correction for HRSD score at T1).

HRSD score at T1 was not significantly correlated with either participant involvement scores (Pearson's r = 0.087, n.s.) or interviewer involvement scores (Pearson's r = 0.204, n.s.).

Involvement behavior

We applied a linear multiple regression design to determine whether the involvement behavior of the participants as measured at T1 contributed to the prediction of severity of depressive symptoms at T2. As we knew that depression score at T1 and participant's gender accounted for some variance in depression score at T2, we controlled for these factors by forcing them into the equation in the first blocks. The factor participant involvement indeed appeared to be a significant predictor of later depression score. Lower levels of participant involvement were associated with worse prognosis (Figure 1, Table 1a).

Since in our hypothesis we took account of the possibility that both low and high involvement may be related to a negative outcome, we also tested for a curvilinear effect of participant involvement. This curvilinear model,

however, yielded a slightly worse fit than the linear model ($F(4,46) = 3.55$, $p = .013$), and the higher-order term (participant involvement squared) did not explain any variance at all ($\Delta R^2 = 0.000$, $\Delta F(1,47) = 0.97$, n.s.)

To check whether the found effect of participant involvement was different for the two sexes, we added an interaction term "gender x participant involvement" to the regression equation. No significant interaction effect was found, however ($\Delta R^2 = 0.023$, $\Delta F(1,47) = 1.41$, n.s.).

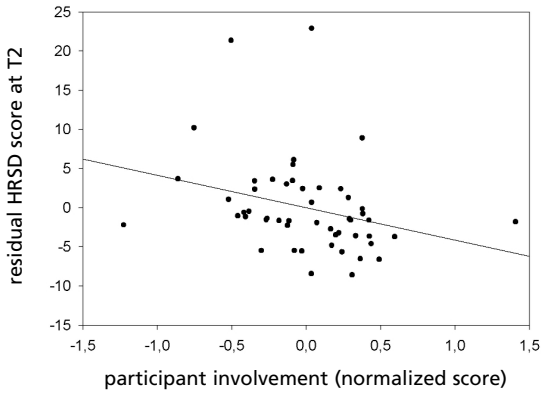

Figure 1 Regression of residual HRSD scores at T2 (corrected for HRSD scores at T1 and gender) on participant involvement scores at T1.

Given the relative high proportion of participants in our sample diagnosed as having a disorder with psychotic features, we were able to investigate whether this subgroup behaved differently from the subgroup without psychotic features. We found that the "psychotic features" group tended to be lower in participant involvement than the "no psychotic features" group (ANOVA; $F(1,49) = 3.22$, $p = .079$). When we controlled for the presence of psychotic features in the equation of Table 1a, however, the factor participant involvement was still predictive of outcome ($\Delta R^2 = 0.083$, $\Delta F(1,46) = 5.11$, $p = .029$). The psychotic features factor did not contribute significantly to the equation.

Table 1 *Summary of regression analyses examining the relationship between involvement behavior at T1 and HRSD score at T2, controlling for HRSD score at T1 and gender*

	Model	ΔR^2	ß	p	F(df)	R^2	p
1a	HRSD score at T1	0.087	0.331	.013	F(3,47)=4.84	0.236	**.005**
	Gender	0.076	-0.303	.022			
	Participant involvement	0.073	-0.272	**.040**			
1b	HRSD score at T1	0.087	0.342	.012	F(5,45)=3.18	0.261	**.015**
	Gender	0.076	-0.309	.021			
	Interviewer involvement	0.001	0.007	.955			
	Participant involvement	0.072	-0.276	**.039**			
	Partic. inv. x Interv. inv.	0.025	-0.161	.222			

In a similar linear regression design (controlling for HRSD score at T1 and gender) we investigated whether the behavior of the interviewer was related to outcome as well. It appeared that the factor interviewer involvement was not predictive of later depression score at all ($\Delta R^2 = 0.001$, $\Delta F(1,47) = 0.03$, n.s.). The six interviewers, however, appeared to differ in their individual levels of involvement behavior (ANOVA, F(5,45) = 3,73, p = .007). Aware of the fact that this could have had repercussions on the levels of their partners' involvement behavior (like participant levels of involvement could have influenced interviewer levels), we checked whether these differences in interviewer style confounded our results. Entering interviewer dummy variables into the equation of Table 1a revealed that this was not the case. The factor participant involvement was still significantly related to outcome ($\Delta R^2 = 0.087$, $\Delta F(1,42) = 4.95$, p = .031). Interviewer dummy variables did not contribute significantly to the equation ($\Delta R^2 = 0.008$, $\Delta F(5,43) = 0.084$, n.s.).

Interaction

Besides investigating whether the behaviors of participant and interviewer separately had predictive qualities, we also examined the interaction between the behaviors of the conversation partners. For that purpose, we regressed the HRSD score at T2 on interviewer involvement, participant involvement, and the interaction term build of these two factors (controlling for HRSD score at

T1 and gender; see Table 1b). As can be seen from the table, this analysis did not yield any new insights. No significant interaction effect was found.

DISCUSSION

In this study, we investigated nonverbal behavioral elements indicative of involvement in remitted depressed patients and their conversation partners. We examined whether this nonverbal involvement behavior was predictive of return of depressive symptoms after 6 months. We found that involvement behavior of the remitted patients was related to outcome. The *lower* the level of involvement displayed, the more unfavorable the prognosis. Involvement behavior of the interviewers was not predictive of later depressive complaints, and no more was the interaction between the conversation partners' behavior.

The finding that low levels of involvement behavior were related to return of depressive symptoms can be seen as an indication of the importance of gratifying social interactions and the role the former patient self plays in these. Fruitful social interactions may need some mutual investment. Social support, considered so important in the protection against depression, is something that one may receive but also largely has to *acquire*. The literature on social support predominantly focuses on the support given by the social environment, disregarding the active stand the needing party itself can take. Displaying some involvement in social interactions may be indispensable for the establishment and maintenance of social supportive relationships. Individuals displaying too little involvement may thus run an increased risk of depression as a result of a decreased social buffer capacity. This idea is in line with more general perspectives that interpersonal strategies involving approach -as opposed to avoidance- can buffer against the depressogenic effects of negative life events by enhancing social resources (cf. Dill and Anderson, 1999; Holahan et al., 1999).

It is instructive to compare the present results with those of previous studies of our research group (Bouhuys and Albersnagel, 1992; Bouhuys and Van den Hoofdakker, 1993; Geerts et al., 1995; Geerts et al., 1996; Geerts and Bouhuys, 1998; Geerts et al., 2000). In these studies involvement was operationalized in exactly the same way as in the present study, but measured when patients were in a depressed state, and used to predict subsequent improvement. When patients' involvement behavior was found to be related

to outcome in these studies, it were the patients displaying the *lowest* levels of involvement that would improve most (Bouhuys and Albersnagel, 1992; Geerts et al., 1995). Low involvement from the part of the interviewers was related to patients' improvement as well (Bouhuys and Van den Hoofdakker 1993; Geerts et al., 1995). Also measures of the interaction between patients' and interviewers' involvement behavior were related to outcome; the degree to which patients and interviewers adjusted their levels of involvement to each other predicted subsequent improvement (Geerts et al., 1996; Geerts and Bouhuys, 1998; Geerts et al., 2000).

The present results clearly deviate from these earlier findings. A favorable outcome was related to the *higher* levels of involvement here, and no interviewer or interaction effects were found. This may indicate that involvement behavior differentially relates to depression maintenance vs. depression relapse, which would be in line with Barnett and Gotlib's observation (1988) that factors predictive of episode duration are not necessarily also predictive of relapse and recurrence. The differences in results may be understood if one recognizes the importance of the difference in the condition of the patients (depressed vs. remitted). Presumably, the way interaction partners *perceive* and *react* to each other's behavior varies depending on the patients' condition. Signs of involvement displayed by patients in a depressed state, for example, may easily be perceived as signs of support seeking and dependency, contributing to these patients being experienced as demanding or claiming (see also Bornstein, 1992). When the depression is over, and the social environment does not face the other in a context of helplessness anymore, these signs of involvement may be perceived as appropriate. Showing higher levels of involvement would be positively received and reacted to in the latter situations, while they would not be so in the first.

The difference in condition may also account for the fact that in this study no significant interviewer or interaction effects were found. Possibly, in a remitted state interaction partners behave more independently than in a depressed state. Indeed, there is evidence that the behaviors of patients and interaction partners are more strongly influenced by each other the more patients are depressed (Bouhuys and Van den Hoofdakker, 1991). The behaviors of the interaction partners in this study may thus have been too weakly associated to find an interviewer or interaction effect on participant's prognosis. This may also be partly a consequence of the fact that the interviewers in the present study probably were not very significant to the

participants compared to people they interact with in daily life (at least now they were not depressed anymore). There is evidence that behavior displayed in patient-stranger interactions is less related to depression outcome than behavior displayed when patients interact with significant others (Hale et al., 1997b; see also Schmaling and Becker, 1991).

The latter fact points to a possible disadvantage of the present design, making the generalizability of the results to everyday life limited. Another factor limiting generalizability may have been the severity of illness of our sample. Our sample consists of inpatients who suffered from severe depression, in many cases accompanied by psychotic features. Clearly, our group cannot straight away be put on a par with, for example, an outpatient group. Other disadvantages of this study are that group size may still not have been large enough, and that medication was not controlled for. Notwithstanding these limitations, this study shows that nonverbal involvement behavior is relevant as a predictor of depressive symptoms, even when measured in remitted patients interacting with relatively insignificant others. This result underpins the importance of behavioral observation in the search for interpersonal risk factors for depression. This method provides a more direct and concrete measure of social functioning than asking participants to reflect on this issue and to fill out a questionnaire. Such behavioral assessments may open new possibilities to unravel processes that underlie inadequate social functioning, and in doing so, bear relevance to prevention of relapse in depression.

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REFERENCES

Aiken LS, West SG (1991) *Multiple regression: Testing and interpreting interactions*. Newbury Park, CA: Sage Publications.

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th ed.)(DSM IV)*. Washington, DC: APA.

Barnett PA, Gotlib IH (1988) Psychosocial functioning and depression: distinguishing among antecedents, concomitants, and consequences. *Psychological Bulletin* 104, 97-126.

Bebbington P (1987) Misery and beyond: the pursuit of disease theories of depression. *International Journal of Social Psychiatry* 33, 13-20.

Bell RA (1987) Social involvement. In *Personality and interpersonal communication*, pp. 195-242. Eds JC McCroskey and JA Daly. Newbury Park, CA: Sage Publications.

Billings AG, Moos RH (1985b) Psychosocial processes of remission in unipolar depression: comparing depressed patients with matched community controls. *Journal of Consulting and Clinical Psychology* 53, 314-325.

Billings AG, Moos RH (1985a) Life stressors and social resources affect posttreatment outcomes among depressed patients. *Journal of Abnormal Psychology* 94, 140-153.

Bornstein RE (1992) The dependent personality: developmental, social, and clinical perspectives. *Psychological Bulletin* 112(1), 3-23.

Bouhuys AL, Albersnagel FA (1992) Do interactional capacities based on observed behaviour interfere with improvement in severely depressed patients? *Journal of Affective Disorders* 25, 107-116.

Bouhuys AL, Jansen JHC, Van den Hoofdakker RH (1991) Analysis of observed behavior displayed by depressed patients during a clinical interview: relationships between behavioral factors and clinical concepts of activation. *Journal of Affective Disorders* 21, 79-88.

Bouhuys AL, Van den Hoofdakker RH (1991) The interrelatedness of observed behavior of depressed patients and of a psychiatrist: an ethological study on mutual influence. *Journal of Affective Disorders* 23, 63-74.

Bouhuys AL, Van den Hoofdakker RH (1993) A longitudinal study of interaction patterns of a psychiatrist and severely depressed patients based on observed behavior: an ethological approach of interpersonal theories of depression. *Journal of Affective Disorders* 27(2), 87-99.

Burgoon JK (1985) Nonverbal signals. In *Handbook of interpersonal communication*, pp. 344-390. Eds ML Knapp and GR Miller. Beverly Hills, CA: Sage Publications.

Burgoon JK, Newton DA, Walther JB, Baesler E (1989) Nonverbal expectancy violations and conversational involvement. *Journal of Nonverbal Behavior* 13, 97-119.

Cahn DD, Frey LR (1992) Listeners' perceived verbal and nonverbal behaviors associated with communicators' perceived understanding and misunderstanding.

Perceptual and Motor Skills 74, 1095-1064.

Cappella JN (1983) Conversational involvement: Approaching and avoiding others. In *Nonverbal interaction*, pp. 37-68. Eds JM Wiemann and RP Harrison. Hillsdale, NJ: Erlbaum.

Cegala DJ, Savage GT, Brunner CC, Conrad AB (1982) An elaboration of the meaning of interaction involvement: toward the development of a theoretical concept. *Communication Monographs* 49, 229-248.

Cohen J (1968) Nominal scale agreement with provision for scaled disagreement of partial credit. *Psychological Bulletin* 70, 213-220.

Coker DA, Burgoon JK (1987) The nature of conversational involvement and nonverbal encoding patterns. *Human Communication Research* 13(4), 463-494.

Coyne JC (1976) Toward an interactional description of depression. *Psychiatry* 39, 28-40.

Coyne JC, Burchill SAL, Stiles WB (1991) An interactional perspective on depression. In *Handbook of Social and Clinical Psychology*, pp. 327-349. Eds CR Snyder and DR Forsyth. Elmsford, NY: Pergamon Press.

Davis D, Holtgraves T (1984) Perceptions of unresponsive others: Attributions, attraction, understandability, and memory of their utterances. *Journal of Experimental Social Psychology* 20, 383-408.

Dill JC, Anderson CA (1999) Loneliness, shyness, and depression: The etiology and interrelationships of everyday problems in living. In *Interactional nature of depression: Advances in interpersonal approaches*, pp. 93-125. Eds TE Joiner and JC Coyne. Washington DC: American Psychological Association.

Geerts E, Bouhuys AL (1998) Multi-level prediction of short-term outcome of depression: The role of nonverbal interpersonal and cognitive processes and of personality traits. *Psychiatry Research* 79, 59-72.

Geerts E, Bouhuys AL, Meesters Y, Jansen JHC (1995) Observed behavior of patients with seasonal affective disorder and an interviewer predicts response to light treatment. *Psychiatry Research* 57, 223-230.

Geerts E, Bouhuys AL, Van den Hoofdakker RH (1996) Nonverbal attunement between depressed patients and an interviewer predicts subsequent improvement. *Journal of Affective Disorders* 40, 15-21.

Geerts E, Bouhuys AL, Bloem GM (1997) Nonverbal support giving induces nonverbal support seeking in depressed patients. *Journal of Clinical Psychology* 53, 41-49.

Geerts E, Kouwert E, Bouhuys N, Meesters Y, Jansen J (2000) Nonverbal interpersonal attunement and extravert personality predict outcome of light treatment in seasonal affective disorder. *Journal of Affective Disorders* 59, 193-204.

Gotlib IH, Hammen CL (1992) *Psychological aspects of depression; Towards a cognitive-interpersonal integration*. Chichester: John Whiley & Sons.

Hale WH, Jansen JHC, Bouhuys AL (1997a) Depression relapse and ethological measures. *Psychiatry Research* 70, 57-64.

Hale WH, Jansen JHC, Bouhuys AL, Jenner JA, Van den Hoofdakker RH (1997b) Non-verbal behavioral interactions of depressed patients with partners and strangers: The role of behavioral social support and involvement in depression persistence. *Journal of Affective Disorders* 44, 111-122.

Hamilton M (1967) Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6, 278-296.

Harlow RE, Cantor N (1994) Social pursuit of academics: Side effects and spillover of strategic reassurance seeking. *Journal of Personality and Social Psychology* 66, 386-397.

Holahan CJ, Moos RH, Bonin LA (1999) Social context and depression: An integrative stress and coping framework. In *Interactional nature of depression: Advances in interpersonal approaches*, pp. 39-63. Eds TE Joiner and JC Coyne. Washington, DC: American Psychological Association.

Joiner TE (2000) Depression's vicious scree: Self-propagating and erosive processes in depression chronicity. *Clinical Psychology: Science and Practice* 7, 203-218.

Lara ME, Klein DN (1999) Psychosocial processes underlying the maintenance and persistence of depression: implications for understanding chronic depression. *Clinical Psychology Review* 19, 553-570.

Lewinsohn PM (1974) Clinical and theoretical aspects of depression. In *Innovative treatment methods in psychopathology*, pp. 63-120. Eds KS Calhoun, HE Adams, and KM Mitchell. New York, NY: Wiley.

Patterson ML (1983) *Nonverbal behavior: A functional perspectiv*e. New York, NY: Springer-Verlag.

Paykel ES (1991) Depression in women. *British Journal of Psychiatry* 158, 22-29.

Paykel ES (1994) Life events, social support and depression. *Acta Psychiatrica Scandinavica* 89, 50-58.

Perris C (1987) Towards an integrating theory of depression focusing on the concept of vulnerability. *Integrative Psychiatry* 5, 27-32.

Robins CJ, Block P (1989) Cognitive theories of depression viewed from a diathesis-stress perspective: Evaluations of the models of Beck and of Abramson, Seligman, and Teasdale. *Cognitive Therapy and Research* 13, 297-313.

Rounsaville BJ, Prusoff BA, Weissman MM (1980) The course of marital disputes in depressed women: A 48-month follow-up study. *Comprehensive Psychiatry* 21, 111-118.

Schmaling K, Becker J (1991) Empirical studies of the interpersonal relations of adult depressives. In *Psychosocial aspects of depression*, pp. 169-185. Eds J Becker and A Kleinman. Hillsdale, NJ: Lawrence Erlbaum Associates.

Segrin C, Abramson LY (1994) Negative reactions to depressive behaviors: A communication theories analysis. *Journal of Abnormal Psychology* 103(4), 655-668.

Segrin C (1998) Interpersonal communication problems associated with depression and

loneliness. In *Handbook of communication and emotion; research, theory, applications, and contexts*, pp. 215-242. Eds PA Anderson and LK Guerrero. San Diego, CA: Academic Press.

Troisi AT, Pasini A, Bersani G, Grispini A, Ciani N (1989) Ethological predictors of amitryptiline response in depressed outpatients. *Journal of Affective Disorders* 17, 129-136.

Weissman MM, Klerman GL (1977) Sex differences and the epidemiology of depression. *Archives of General Psychiatry* 34, 98-111.

Zeiss AM, Lewinsohn PM (1988) Enduring deficits after remissions of depression: A test of the scar hypothesis. *Behaviour Research and Therapy* 26, 151-158.

3

Cognitive, physiological, and personality correlates of recurrence of depression

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ABSTRACT

Background

The risk of recurrence in depressive disorder is high and increases with the number of episodes. We investigated whether individuals with a history of recurrent depression deviate from individuals with a single episode, as regards risk-related variables in 3 different fields of depression research.

Methods

Participants were 102 outpatients with major depressive disorder remitted from an episode (60 recurrent, 42 nonrecurrent). We assessed the perception of emotions from vocal stimuli, 24-h urinary free cortisol, and neuroticism.

Results

The recurrent group had higher cortisol levels than the nonrecurrent group, and recurrent women also had a more negative perception than nonrecurrent women. These results were independent of each other, and could also not be accounted for by neuroticism or residual symptoms. Gender differences were found in all 3 fields.

Limitations

The cross-sectional design limits the possibility to draw conclusions on the causality of the observed effects.

Conclusions

Remitted outpatients with recurrent depression deviate from remitted outpatients with single episode depression as regards physiology and social cognition, in a way that may increase their risk of the development of subsequent episodes. The results may have implications for prophylactic treatment strategies.

INTRODUCTION

Depression is a heterogeneous disease, both in its manifestations and its etiology. In spite of this heterogeneity, research on depressive disorder is most often monodisciplinary. Research that crosses boundaries between disciplines is rare, which precludes an integrated understanding of depression (see also Costello et al., 2002). In the present study we have simultaneously examined differences in social cognition (emotion perception), physiology (cortisol), and personality (neuroticism) between patients remitted from a first episode of depression and patients remitted from a recurrent episode. Recurrence is a major problem in depressive disorder. The likelihood of recurrence after a first episode may be greater than 40% (Angst, 1999) and seems to increase with subsequent episodes (Haghighat, 1996). Individual differences in social cognition, physiology, or personality might be involved in the risk of recurrence.

In the field of social cognition we investigated the perception of emotions from vocal stimuli (affective prosody). Emotion perception in depression has been found to be impaired (e.g., Mikhailova et al., 1996; Surguladze et al., 2004), and to be negatively biased (e.g., Gur et al., 1992; Surguladze et al., 2004). A negative perceptual bias has also been related to an unfavorable course of the depression (Geerts and Bouhuys, 1998; Bouhuys et al., 1999a; Bouhuys et al., 1999b). Most studies used facial expressions as stimuli, but two studies using vocal expressions also found impaired emotion recognition in depressives (Murphy and Cutting, 1990; Emerson et al., 1999). Studies of remitted individuals are scarce. We found 2 studies (faces), both showing some recovery of perceptual deficits in remission (Mikhailova et al., 1996; Bouhuys et al., 1999b), although a negative perceptual bias was still predictive of relapse in the Bouhuys study. No studies of the perception of vocal expressions have been done in remitted individuals, one reason for us to do so.

In the field of physiology we investigated cortisol, a hormone involved in the stress response. Many depressed patients show increased cortisol secretion, as a result of an overactive hypothalamic-pituitary-adrenal (HPA) axis (Thase and Howland, 1995). When patients recover, cortisol levels return to normal values (Plotsky et al., 1998). Some studies, however, show that HPA-axis hyperactivity can become permanent when patients experience several episodes (Gurguis et al., 1990). Such persistent HPA-axis hyperactivity may in turn constitute a risk for the development of subsequent episodes (e.g., Targum, 1984; Zobel et al., 2001).

In the field of personality we investigated neuroticism. This concept refers to "a broad dimension of individual differences in the tendency to experience negative, distressing emotions and to possess associated behavioral and cognitive traits" (Costa and McCrae, 1987). Neuroticism is associated with a higher risk of onset of depression, with more severe episodes, and with a more unfavorable outcome (Klein et al., 2002; Ormel et al., 2004a). Although neuroticism has a state-dependent component, neuroticism scores of remitted individuals are still higher than those of never-depressed individuals (Maier et al., 1992; Ormel et al., 2004b), and also predict subsequent episodes (Faravelli et al., 1986; Duggan et al., 1990; Surtees and Wainwright, 1996).

A few studies point to interrelations between the 3 variables that are the focus of the present study (emotion perception, cortisol, neuroticism). There is evidence that hypercortisolism impairs cognitive functioning (Lupien and McEwen, 1997). One study specifically reports high cortisol levels to be associated with a negative bias in memory for facial expressions (Van Honk et al., 2003). There is also some evidence that neuroticism is related to a negative cognitive bias, although results are not consistent (Rusting, 1998). Of the 2 studies that specifically focus on the relation between neuroticism and emotion perception (faces), one reports no relation (McCown et al., 1989), while the other reports a positive relation with regard to the perception of ambiguous stimuli (Geerts and Bouhuys, 1998). Finally, there is some evidence that neuroticism is linked with increased cortisol levels in response to stress (Kirschbaum et al., 1995; Zobel et al., 2004). Other studies, however, found the opposite (McCleery and Goodwin, 2001) or did not found any relation between neuroticism and cortisol at all (Roy, 1996).

In the present study, we have compared remitted outpatients having a history of recurrent depression with remitted outpatients who experienced a single episode. We expected recurrent individuals to be more impaired in their emotion recognition and/or to have a more negative perceptual bias as compared to nonrecurrent individuals; to have higher cortisol levels; and to have higher neuroticism scores. We investigated whether differences in one field are related to differences in the other fields. We also examined possible gender differences (cf. Lynn and Martin, 1997; Shamim, 2000; Hall et al., 2000).

METHODS

Participants

The present study is part of a larger study on predictors of future recurrence. The original sample consisted of 208 outpatients who, according to their practitioners, were remitted from a depressive episode. After their written informed consent subjects were screened with the Composite International Diagnostic Interview (CIDI, lifetime version; World Health Organization, 1997). They were included in the study if they met DSM-IV criteria for major depressive disorder or dysthymic disorder (American Psychiatric Association, 1994). Exclusion criteria were: major depressive disorder with psychotic symptoms, substance dependence, organic cause of the disorder, dysfunction of the CNS, severe communication problems, age not between 18 and 66, and index episode more than 6 months ago. Our remission criterion was: a BDI score (Beck Depression Inventory; Beck and Steer, 1987) of 8 or less for 2 consecutive times, with a 4-week interval in between (cf. Frank et al., 1991). Thirty-five (16.8%) of the 208 participants were excluded from the study because of one of the exclusion criteria. Nine subjects (4.3%) preliminarily withdrew. Sixty subjects (28.8%) failed to satisfy our remission criterion, also in the long run (subjects were contacted for up to 2 years). All in all, 104 participants remained (50.0%).

The sample of 104 participants was divided into a "recurrent" (n = 60) and a "nonrecurrent" group (n = 42) according to the CIDI diagnosis. Two subjects suffering from dysthymic disorder were excluded from the analyses of the present study. General characteristics of the final sample (n = 102) are presented in Table 1. The recurrent and the nonrecurrent group had similar gender ratios (57% vs. 62% female, Chi-square test, n.s.). Age, however, was higher in the recurrent group (ANOVA; $F(1,100) = 7.97$, $p < .01$), and educational level tended to be higher in this group (Mann-Whitney U test, $Z = -1.74$, $p < .10$), which stressed the need to control for age and education in the statistical analyses. The groups did not differ on any of the other variables presented in Table 1.

Data collection

Data collection sessions took place between April 1999 and April 2002, in the daytime, and included interviews, questionnaires, and computer tasks. One of the interviews was an HRSD interview (Hamilton Rating Scale for Depression,

Table 1 *Sample characteristics (n = 102)*

Female, n (%)	61 (60%)
Age, mean (SD)	44.6 (10.8)
Educational level, median	Secondary vocational
BDI score, mean (SD)	3.7 (2.3)
Remission period, median (IQR)	77 days (74.5)
Age onset, mean (SD)	30.7 (12.1)
Psychoactive medication, n [length of use, median (IQR)]	
Antidepressants	55 [29.9 weeks (48.7)]
Sedatives	18 [60.4 weeks (322.3)]
Mood Stabilizers	6 [44.4 weeks (77.2)]

IQR = interquartile range

21-item version; Hamilton, 1967), assessed to obtain an external judgment of residual symptom severity. The mean HRSD score was 4.5 (SD = 3.2, range 0–15). Recurrent and nonrecurrent individuals did not differ in HRSD score (ANOVA, n.s.). At the end of the session, participants were given a booklet with self-report questionnaires to fill out at home. One of the questionnaires was the Eysenck Personality Questionnaire (Revised Short Scale (EPQ-RSS), Sanderman et al., 1995), a 24-item scale from which neuroticism and extraversion scores can be derived. The neuroticism subscale consisted of 12 items.

Prosody task

The affective prosody task was developed recently for lack of a suitable task in the Dutch language. The task consists of 2 subtasks: an emotion task and a control task. The control task serves to determine whether differences detected in the emotion task are emotion specific and not due to general cognitive or hearing disturbances. The control task consists of 18 sentences, expressed in a neutral, inquiring, or affirming tone of voice. The emotion task consists of 36 sentences expressed in a fearful, sad, angry, surprised, happy, or neutral tone of voice. The stimuli are 3 different sentences in Dutch intended to be linguistically neutral, expressed by 2 actors: 1 male and 1 female. The stimuli are presented in random order via the speakers of a computer. Subjects are asked to decide which of the above-mentioned 6 emotions is expressed in the sentences.

Analyses were divided into a "recognition part" and an "interpretation part". The recognition part deals with whether the expressions were identified correctly. The interpretation part deals with how an expression was interpreted when it was identified incorrectly. This part was intended to detect possible perceptual bias. To this end, we pooled the incorrect responses that were negative (fearful, angry, sad) and those that were non-negative (happy, surprised, neutral), regardless of the valence of the presented stimulus. These pooled scores were adjusted for the overall number of incorrect responses. Since the fractions of incorrect responses in the negative and the non-negative direction are complementary, we will only present the results on the negative incorrect responses.

Cortisol

Participants were asked to collect their urine the day after the measurement session from 5:00 p.m. until 5:00 p.m. the next day. The volume ranged from 460 to 5900 ml (M = 2071 ml, SD = 961). Urine samples were kept frozen at -20°C until assays were done. Cortisol was measured by radioimmunoassay (RIA) with locally prepared rabbit antiserum. It was purified on Sep-pack columns and isolated on Sephadex LH-20 columns. Using this method, cortisol levels of normal volunteers have been found to range from 30–260 nmol/24h, most individuals having values between 50 and 100 nmol/24h. Cortisol scores were log-distributed. Therefore, statistical testing was done on log-transformed data.

Data analysis

We used a two-way ANCOVA design with group (recurrent/nonrecurrent) and gender as between-factors. For the recognition part of the prosody task we used a two-way MANCOVA design with repeated measures on the different emotions. Logistic regression analyses were done to test whether differences between the recurrent and the nonrecurrent group in the different fields could be accounted for by each other. The predictor variables in the logistic analyses were z-transformed for ease of comparison of the effects. In all analyses, we adjusted for age and level of education.

RESULTS

Missing data

The number of missing data on the variables of the different fields was differential, leaving 97 participants for the analyses on affective prosody (41 nonrecurrent and 56 recurrent); 81 participants on cortisol (35 nonrecurrent and 46 recurrent); and 101 participants on neuroticism (41 nonrecurrent, 60 recurrent). In the multivariate analyses with variables of all 3 fields, the number of valid cases was 76 (33 nonrecurrent, 43 recurrent).

Affective prosody

The control part of the prosody task was done rather well (16.1 of 18 stimuli identified correctly (89.4%)). The recurrent and the nonrecurrent group did not perform differently on this part of the task ($F(1,91) = 0.75$, n.s.), and there was no gender difference ($F(1,91) = 1.20$, n.s.) or group by gender interaction ($F(1,91) = 0.90$, n.s.). Hence, when differences between the groups are found in the emotion part of the task, they can be considered emotion specific. Table 2 shows the responses on the emotion part. The percentage of correctly identified emotions ranged from 35.2% to 84.0%. Happy and fearful expressions were misidentified most often, while angry and neutral expressions were recognized best. This pattern of recognition is fairly in line with what is found in studies of healthy individuals (e.g., Johnson et al., 1986). Overall recognition was 60.3% (21.7 of 36 stimuli identified correctly), which is well beyond

Table 2 *Responses to 6 emotional stimuli in an affective prosody task*

		Response					
		"Fearful"	"Sad"	"Angry"	"Surprised"	"Happy"	"Neutral"
Stimulus	Fearful	**40.7** (24.8)	8.8 (12.2)	3.4 (7.6)	27.3 (21.8)	11.9 (13.2)	7.9 (13.0)
	Sad	6.0 (13.9)	**61.2** (31.7)	0.7 (3.3)	5.3 (10.4)	0.5 (5.1)	26.3 (27.0)
	Angry	2.7 (10.1)	1.2 (6.0)	**84.0** (19.5)	3.4 (7.6)	1.9 (6.3)	6.7 (10.4)
	Surprised	3.2 (7.5)	2.1 (6.0)	1.0 (4.7)	**56.9** (23.3)	19.9 (19.6)	16.8 (17.1)
	Happy	4.5 (9.2)	0.9 (3.7)	8.6 (11.8)	35.1 (23.0)	**35.2** (20.3)	15.8 (14.9)
	Neutral	0.9 (4.4)	8.9 (14.0)	1.7 (5.6)	4.0 (9.2)	1.4 (4.6)	**83.2** (19.2)

Means (SDs) in percentages. In bold: mean percentages of correct responses. Number of trials = 36. n = 97.

chance level. The recurrent and the nonrecurrent group performed equally well (F(1,91) = 0.52, n.s.), and did not perform differently on the different emotions (F(5,87) = 0.40, n.s.). Nor was the interaction between group and gender significant (F(1,91) = 0.01, n.s.). Women, however, generally performed better than men (63.9% vs. 54.8% correct responses; F(1,91) = 19.79, p < .001). The interaction between gender and emotion was not significant (F(5,87) = 2.08, n.s.).

We subsequently investigated how subjects interpreted the expressions when they did not correctly identify the emotion. We therefore analyzed the incorrect responses pooled according to valence (negative vs. non-negative). Group and gender effects were not significant in this analysis (F(1,91) = 1.00, n.s. and F(1,91) = 0.02, n.s.), but the interaction between group and gender was (F(1,91) = 4.90, p < .05, see Figure 1A). Analyses within gender revealed that recurrent women interpreted the stimuli in a negative direction more often than nonrecurrent women did (F(1,53) = 6.37, p < .05; n = 57, 23 nonrecurrent, 34 recurrent). In men, the difference was not significant (F(1,36) = 1.07, n.s.; n = 40, 18 nonrecurrent, 22 recurrent).

Cortisol

Cortisol results are depicted in Figure 1B. The recurrent group showed significantly higher cortisol levels than the nonrecurrent group (F(1,75) = 4.10, p < .05). The untransformed median for the recurrent group was 90.0, for the

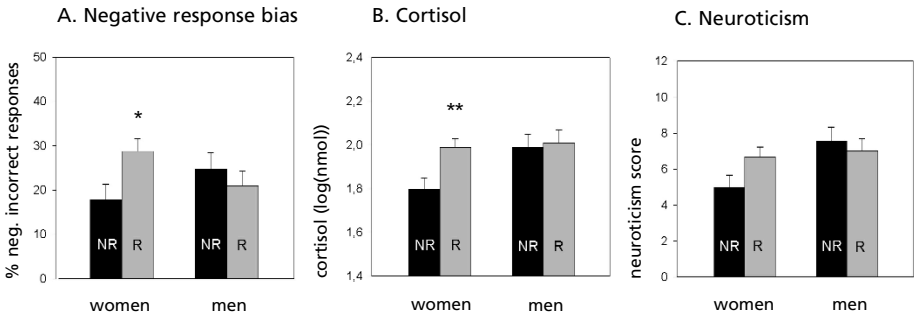

Figure 1 Differences between recurrent (R) and nonrecurrent (NR) groups by gender. A. Negative incorrect responses on an affective prosody task. B. 24-h urinary free cortisol levels (log-transformed). C. Neuroticism scores. * p < .05. ** p < .001.

non-recurrent group 77.9. The interaction between group and gender revealed a trend ($F(1,75) = 3.13$, $p < .10$). Within-gender analyses showed that the difference between the recurrent and the nonrecurrent group was highly significant in women ($F(1,49) = 11.78$, $p < .001$; n = 53, 21 nonrecurrent, 32 recurrent) and not significant in men ($F(1,24) = 0.15$, n.s.; n = 28, 14 nonrecurrent, 14 recurrent). Generally, cortisol levels were higher in men than in women (untransformed medians 93.5 and 79.6, respectively; $F(1,75) = 4.92$, $p < .05$).

Neuroticism

Recurrent and nonrecurrent individuals did not show different neuroticism scores (overall group effect $F(1,95) = 0.66$, n.s.; interaction group by gender $F(1,95) = 2.72$, n.s.; see Figure 1C). Men, however, had higher neuroticism scores than women ($F(1,95) = 4.50$, $p < .05$). The mean score for men was 7.2 (SD = 3.2), for women 6.1 (SD = 3.3). Scores of both sexes were above those of norm groups (male control group score 3.2 (SD = 3.0), female control group score 4.6 (SD = 3.3); Sanderman et al., 1995).

Multivariate analyses

To investigate whether the findings in the different fields could be explained by one another, we first made a correlation matrix for the relevant variables (negative incorrect responses, cortisol, and neuroticism). The correlations were all very small and not significant (partial r's: 0.016, 0.069, and -0.004, n.s.). The result was not much different when correlation matrices were made for men and women separately. This suggests that the differences between the recurrent and the nonrecurrent group in the one field cannot be explained by differences in the other fields. This was confirmed by logistic regression analysis, done in the female subgroup (see Table 3). The table shows that the effect of the negative incorrect responses was reduced to a trend. This was a result of the reduced number of cases in this multivariate analysis rather than a result of the presence of the other variables. Cortisol levels were associated most strongly with recurrence in this model. Neuroticism scores did not contribute to the model significantly.

Residual symptom severity

Since it can be argued that the differences found in this study may be due to differences in residual symptoms, we checked whether the results would have been different when HRSD depression score was controlled for. None of the

observed effects lost its significance as a result. We concluded that our findings are not confounded by residual symptom severity.

Table 3 *Summary of multivariate logistic regression analysis for variables associated with recurrence in women*

Variables	OR	95% CI		p
		Lower	Upper	
Age	3.54	1.23	10.19	.019
Education	2.71	1.15	6.39	.023
Negative incorrect responses	2.88	1.00	8.30	.051
Cortisol (log)	4.64	1.54	13.96	.006
Neuroticism	1.87	0.77	4.51	.164

Test results for z-transformed variables; n = 50 women (20 nonrecurrent, 30 recurrent).

DISCUSSION

This study showed that, in remitted outpatients, a history of recurrent depression is associated with higher cortisol levels and in women also with a more negative auditory perception. These findings could not be accounted for by one another, and also not by neuroticism or residual symptoms.

Since our study was cross-sectional, we cannot say whether the observed differences result from the experience of former episodes (scars) or whether they existed beforehand (premorbid vulnerability). Admittedly, this is a limitation of the study. Both scar and premorbid vulnerability, however, may account for increased risk of recurrence. A negative perceptual bias, for example, presumably hampers social interaction (Gotlib and Hammen, 1992). Problematic social interactions in turn increase risk of depressive symptomatology (Joiner and Coyne, 1999). Indeed, a negative bias in the perception of facial expressions is related to persistence of depression (Bouhuys et al., 1999a), as well as to depression relapse (Bouhuys et al., 1999b). Our finding that recurrent individuals are more negative in their perception of vocal expressions than nonrecurrent individuals fits this pattern as well.

Our finding on the relatively negative perception of recurrent individuals

was confined to the subgroup of women. This was also the case in the study by Bouhuys et al. (1999a). This gender specificity is in line with the notion that social cognitions play a major role especially in women's depression, as women are more sensitive to interpersonal affairs (Nolen-Hoeksema, 2002). Our finding that women did better than men on emotion recognition is in accordance with findings in healthy individuals that women are generally superior decoders of nonverbal cues (Hall et al., 2000).

The relatively high cortisol levels we found in the recurrent group may be a reflection of a persistent hyperactivity of the HPA axis, as was previously observed in individuals who experienced multiple depressive episodes (Gurguis et al., 1990). The stress-response system may have become permanently hypersensitive in these individuals, as a result of long-lasting changes in its modulatory pathways (Post, 1992). As a consequence, minor stressors can induce exaggerated physiological stress responses. This may set these individuals at increased risk of becoming depressed again (Post, 1992). Thus far, increased risk of recurrence in relation to HPA-axis hyperactivity was only found in studies using challenge tests (e.g., Targum, 1984; Zobel et al., 2001). To our knowledge, ours is the first study in which elevated levels of 24-h urinary free cortisol were found to be associated with recurrence of depression.

Although the difference in cortisol levels applied to the whole sample, the difference again was most pronounced in women. Zobel et al. (2001) also report their findings to be strongest in women. This fits in with the notion that dysregulation of the HPA axis is more likely in women, possibly due to a modulating role of gonadal hormones (Young and Korszun, 1999). We also found that cortisol levels were higher in men than in women. Similar gender differences are reported to exist in healthy samples (Shamim et al., 2000), although this difference seems to reverse with older age (Goldman et al., 2004).

We did not find a difference in neuroticism between recurrent and nonrecurrent individuals. One reason for this unexpected result may be that the experience of a depressive episode does not seem to bring about a persistent increase in neuroticism (e.g., Ormel et al., 2004b). Part of the expected deviations in recurrent individuals, i.e. that caused by scars induced by previous episodes, therefore may not hold for neuroticism. Another explanation is that the distinction between the recurrent and the nonrecurrent group may have been blurred by the presence of nonrecurrent individuals

who will become recurrently depressed in the future. The fact that neuroticism scores in both the recurrent and the nonrecurrent group were above norm scores reinforces this idea.

Our finding that men showed higher neuroticism scores than women is also unexpected. In the general population women tend to have higher neuroticism scores (Lynn and Martin, 1997). Whether our finding is characteristic for remitted depressed samples is not clear. The relevant literature rarely presents gender-specific data. A possible explanation for our finding may be that, since men become depressed less easily than women, men who do become depressed are on average more neurotic than women who develop depression.

A strong feature of our study was that we took measurements in different fields of investigation in the same subjects. We found that the differences in the cognitive and the physiological field could not be accounted for by one another. Negative incorrect responses and cortisol levels were not related to each other at all. This finding seems inconsistent with evidence that high cortisol levels affect cognitive functioning (Lupien and McEwen, 1997). This evidence, however, mainly concerns memory and attention, in tasks with non-emotional stimuli. Neuroticism scores were also not related to the variables in the other fields. The number of studies that report on such relationships is small and results are not consistent (see introduction). These inconsistencies may be the result of differences in methodology. For example, urinary free cortisol levels may be too crude a measure to assess slight HPA-axis dysregulations, whereas challenge tests may be able to detect these. Another limitation of the present study was that medication use was not controlled. The recurrent and the nonrecurrent group, however, did not statistically differ in medication use.

Our results suggest that a negative perceptual bias and elevated basal cortisol levels are independent correlates of recurrence of depression, and are not merely manifestations of neuroticism. Since it is likely that these factors also increase risk of subsequent episodes, the findings are potentially relevant for prophylactic treatment strategies.

REFERENCES

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th ed.) (DSM IV)*. Washington, DC: APA.

Angst J (1999) Major depression in 1998: are we providing optimal therapy? *Journal of Clinical Psychiatry* 60(6), 5-9.

Beck AT, Steer RA (1987) *Beck Depression Inventory; Manual*. New York, NY: Harcourt Brace Janovich.

Bouhuys AL, Geerts E, Gordijn MC (1999a) Gender-specific mechanisms associated with outcome of depression: perception of emotions, coping and interpersonal functioning. *Psychiatry Research* 85, 247-261.

Bouhuys AL, Geerts E, Gordijn MC (1999b) Depressed patients' perception of facial emotions in depressed and remitted state is associated with relapse: a longitudinal study. *Journal of Nervous and Mental Disease* 187, 595-602.

Costa PT, McCrae RR (1987) Neuroticism, somatic complaints, and disease: Is the bark worse than the bite? *Journal of Personality* 55, 299-316.

Costello EJ, Pine DS, Hammen C, March JS, Plotsky PM, Weissman MM, Biederman J, Goldsmith HH, Kaufman J, Lewinsohn PM, Hellander M, Hoagwood K, Koretz DS, Nelson CA, Leckman JF (2002) Development and natural history of mood disorders. *Biological Psychiatry* 52, 529-542.

Duggan CF, Lee AS, Murray RM (1990) Does personality predict long-term outcome in depression? *British Journal of Psychiatry* 157, 19-24.

Emerson CS, Harrison DW, Everhart DE (1999) Investigation of receptive affective prosodic ability in school-aged boys with and without depression. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 12, 102-109.

Faravelli C, Ambonetti A, Pallanti S, Pazzagli A (1986) Depressive relapses and incomplete recovery from index episode. *American Journal of Psychiatry* 7, 888-891.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48, 851-855.

Geerts E, Bouhuys AL (1998) Multi-level prediction of short-term outcome of depression: the role of nonverbal interpersonal and cognitive processes and of personality traits. *Psychiatry Research* 79, 59-72.

Goldman N, Weinstein M, Cornman J, Singer B, Seeman T, Ming-Cheng C (2004) Sex differentials in biological risk factors for chronic disease: estimates from population-based surveys. *Journal of Women's Health* 13, 393-403.

Gotlib IH, Hammen CL (1992) Toward a cognitive-interpersonal conceptualization of depression. In *Psychological aspects of depression; Toward a cognitive-interpersonal integration*, pp. 245-267. Chichester: John Whiley & Sons.

Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg C, Kraemer HC (1992) Facial emotion

discrimination: II. Behavioral findings in depression. *Psychiatry Research* 41, 241-251.
Gurguis GN, Meador-Woodruff JH, Haskett RF, Greden JF (1990) Multiplicity of depressive episodes: phenomenological and neuroendocrine correlates. *Biological Psychiatry* 27, 1156-1164.
Haghighat R (1996) Lifelong development of risk of recurrence in depressive disorders. *Journal of Affective Disorders* 41, 141-147.
Hall JA, Carter JD, Horgan TG (2000) Gender differences in nonverbal communication of emotion. In *Gender and emotion: Social psychological perspectives*, pp. 97-117. Ed AH Fischer. New York, NY: Cambridge University Press.
Hamilton M (1967) Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6, 278-296.
Johnson WF, Emde RN, Scherer KR, Klinnert MD (1986) Recognition of emotion from vocal cues. *Archives of General Psychiatry* 43, 280-283.
Joiner TE, Coyne JC (1999) *The interactional nature of depression: Advances in interpersonal approaches*. Washington, DC: American Psychological Association.
Kirschbaum C, Prussner JC, Stone AA, Federenko I, Gaab J, Lintz D, Schommer N, Hellhammer DH (1995) Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosomatic Medicine* 57, 468-474.
Klein DN, Durbin CE, Shankman SA, Santiago NJ (2002) Depression and personality. In *Handbook of depression*, pp. 115-140. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.
Lupien SJ, McEwen BS (1997) The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research Reviews* 24, 1-27.
Lynn R, Martin T (1997) Gender differences in extraversion, neuroticism, and psychoticism in 37 nations. *Journal of Social Psychology* 137, 369-373.
Maier W, Lichtermann D, Minges J, Heun R (1992) Personality traits in subjects at risk for unipolar major depression: a family study perspective. *Journal of Affective Disorders* 24, 153-163.
McCleery JM, Goodwin GM (2001) High and low neuroticism predict different cortisol responses to the combined dexamethasone/CRH test. *Biological Psychiatry* 49, 410-415.
McCown WG, Dewolfe A, Shack J, Maier R (1989) Role of method of stimulus presentation in research on recognition of facial affect. *Perceptual and Motor Skills* 68, 1095-1098.
Mikhailova ES, Vladimirova TV, Iznak AF, Tsusulkovskaya EJ, Sushko NV (1996) Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. *Biological Psychiatry* 40, 697-705.
Murphy D, Cutting J (1990) Prosodic comprehension and expression in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry* 53, 727-730.

Nolen-Hoeksema S (2002) Gender differences in depression. In *Handbook of depression*, pp. 492-509. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Ormel J, Rosmalen J, Farmer A (2004a) Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* 39, 906-912.

Ormel J, Oldehinkel AJ, Vollebergh W (2004b) Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Archives of General Psychiatry* 61, 990-996.

Plotsky PM, Owens MJ, Nemeroff CB (1998) Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatric Clinics of North America* 21, 293-307.

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry* 149, 999-1010.

Roy A (1996) HPA axis function and temperament in depression: a negative report. *Biological Psychiatry* 39, 364-366.

Rusting CL (1998) Personality, mood, and cognitive processing of emotional information: Three conceptual frameworks. *Psychological Bulletin* 124, 165-196.

Sanderman R, Arrindell WA, Ranchor AV, Eysenck HJ, Eysenck SBG (1995) *Het meten van persoonlijkheidskenmerken met de Eysenck Personality Questionnaire (EPQ). Een handleiding*. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.

Shamim W, Yousufuddin M, Bakhai A, Coats AJ, Honour JW (2000) Gender differences in the urinary excretion rates of cortisol and androgen metabolites. *Annals of Clinical Biochemistry* 37, 770-774.

Surguladze SA, Young AW, Senior C, Brebion G, Travis MJ, Phillips ML (2004) Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology* 18, 212-218.

Surtees PG, Wainwright NW (1996) Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. *British Journal of Psychiatry* 169, 338-347.

Targum SD (1984) Persistent neuroendocrine dysregulation in major depressive disorder: a marker for early relapse. *Biological Psychiatry* 19, 305-318.

Thase ME, Howland RH (1995) Biological processes in depression: An updated review and integration. In *Handbook of depression (2nd ed.)*, pp. 213-279. Eds EE Beckham and WR Leber. New York, NY: Guilford Press.

Van Honk J, Kessels RP, Putman P, Jager G, Koppeschaar HP, Postma A (2003) Attentionally modulated effects of cortisol and mood on memory for emotional faces in healthy young males. *Psychoneuroendocrinology* 28, 941-948.

World Health Organization (1997) *Composite International Diagnostic Interview (CIDI), version 2.1. Dutch translation and revision*. Amsterdam: AMC.

Young E, Korszun A (1999) Women, stress, and depression: Sex differences in hypothalamic-pituitary-adrenal axis regulation. In *Gender differences in mood and*

anxiety disorders: From bench to bedside. Review of psychiatry series, Vol. 18, No. 3, pp. 31-52. Ed E Leibenluft. Washington, DC: APA.

Zobel A, Barkow K, Schulze-Rauschenbach S, Von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W (2004) High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatrica Scandinavica* 109, 392-399.

Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001) Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. *Journal of Psychiatric Research* 35, 83-94.

4

The assocation between levels of cortisol secretion and fear perception in patients with remitted depression predicts recurrence

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ABSTRACT

Aim

This study examines the association between cortisol secretion and fear perception in remitted patients, in order to identify mechanisms underlying risk for recurrence of depression. We hypothesized that the stronger the association between cortisol secretion and fear perception in persons with remitted depression, the more recurrence will be experienced. We also investigated whether high levels of cortisol and fear perception per se predict more recurrence. These effects were assumed to be stronger in women than in men.

Methods

In a prospective design we investigated 77 outpatients with remitted depression and related the association between their 24-h urinary free cortisol secretion and fear perception (from ambiguous faces and from vocal expressions) to recurrence of depression within 2 years. We applied Cox regression models, partial correlations, and Fisher's z tests.

Results

In 21 patients depression recurred. Irrespective the channel of perception (eye or ear), the interaction between fear perception and cortisol secretion was significantly related to recurrence of depression. Patients high or low on both variables were more at risk. This increased risk was also reflected by a significant association between cortisol secretion and facial fear perception, but only among subjects who experienced recurrence. A trend in the same direction was found for vocal fear perception. Fear perception and cortisol secretion per se did not predict recurrence. No gender differences were found.

Conclusion

The association between cortisol secretion and fear perception (probably indicative for altered fear circuits in the brain) constitutes a mechanism underlying risk for recurrence of depression.

INTRODUCTION

Recurrence rates of depression after recovery are high, incurring considerable social and financial costs (Angst, 1999; Pincus and Pettit, 2001; Crown et al., 2002). Therefore, identification of risk factors for recurrence is important.

Differential regulation of the hypothalamic-pituitary-adrenal (HPA) axis has been presumed to constitute risk for depression (Holsboer, 2000). During the depressed state, cortisol secretion is increased in most of the patients with severe depression. The likelihood that HPA-axis hyperactivity becomes permanent is higher when patients suffered several episodes (Gurguis et al., 2004; Bos et al., 2005). Such persistent HPA-axis hyperactivity may in turn set persons at risk for recurrence (Ribeiro et al., 1993; Zobel et al., 1999; Zobel et al., 2001).

Vulnerability to depression in some individuals may be a consequence of a diathesis–stress process in which maladaptive interpersonal skills and cognitive representations of the self and others in relationships are diatheses (Joiner and Coyne, 1999). Individuals having a negative bias in the perception of their social environment may experience more stress. This increases the likelihood that stressful interpersonal events occur, resulting in more recurrence of depression (Hammen, 1992; Segal et al., 1996). The perception of (schematic) facial expressions of emotions seems to be a good model to assess a negative bias. Such bias has been frequently demonstrated in depressed patients (see for instance Mandal and Bhattacharya, 1985; Gur et al., 1992; Rubinow and Post, 1992; George et al., 1998; Hale et al., 1998; Gotlib et al., 2004), and has been found to be linked to unfavorable outcome of depression (Bouhuys et al., 1999a) and to relapse (Bouhuys et al., 1999b).

Empirical evidence from studies of animals and healthy persons has linked cortisol secretion to the processing of threatening stimuli and to amygdalar activity in the brain (Adolphs, 2002; LeDoux, 2003; Shinnick-Gallagher et al., 2003). Together with the above described differential neuroendocrine and cognitive function in depression, this linkage between fear perception and cortisol secretion prompted us to hypothesize that depressed and control subjects may differ in this respect (Bouhuys et al., 2005). Indeed, we found that cortisol secretion was specifically related to facial fear perception in depressed women, whereas overall levels of cortisol and perception of fear did not differ between depressed and control subjects. We interpreted these findings in terms of depressed women having developed sensitive fear circuits

in which cortisol and fear perception have become directly linked. We supposed that this association constitutes a gender-specific mechanism underlying risk for depression. To test this presumption more soundly, we investigated this association *prospectively*, and studied perception of fear from both visual and auditory stimuli.

We hypothesized that the stronger the association between 24-h cortisol secretion and perception of fear in patients with remitted depression will be, the more recurrence will be suffered within 2 years, and that this is more true for women than for men. We also investigated whether higher levels of cortisol and fear perception per se predict more recurrence. In addition, we explored whether putative risk of recurrence connected to the one type of fear perception can be explained by the other type.

METHODS

Participants

We investigated 77 outpatients with remitted depression. These patients form a subgroup of 104 patients who participated in a larger longitudinal study on predictors of recurrence of depression. After patients had given informed consent, their attendants' diagnosis was independently confirmed (Composite International Diagnostic Interview (CIDI, lifetime version). Patients between 18 and 65 years with major depressive disorder (MDD) or dysthymia were included (DSM-IV; American Psychiatric Association, 1994), if their index episode was less than 6 months ago and they had no missing data on the neuroendocrine and cognitive measures (see further). Persons with psychotic symptoms, a dysfunction of the CNS, substance dependence, an organic cause of the disorder, or severe communication problems were excluded.

Seventy-five participants were remitted from MDD, 2 participants were remitted from dysthymia. Fourteen participants suffered from "double depression" and 26 participants experienced comorbid anxiety. Forty-two of the participants with MDD had a history of recurrent depression, 33 had had a single episode. The group consisted of 51 women and 26 men. Their mean age at baseline (T0) was 44.0 years ± 10.8 (SD), range 24–65 years.

After inclusion, participants' severity of depression was assessed 4-weekly with the Beck Depression Inventory (BDI, Beck et al., 1961). We considered patients remitted who scored 8 or less for two consecutive times (Frank et al.,

1991). Once remission was established, baseline assessments were performed (T0), consisting among other things of a Hamilton Rating Scale for Depression interview (HRSD; Hamilton, 1967), two cognitive tasks, and a cortisol measurement.

After the baseline assessments the participants completed the BDI on a 4-weeks basis during a 2-year follow-up. If BDI scores exceeded 14 for 2 consecutive times (see Frank et al., 1991), the CIDI (12-months version) was conducted to establish recurrence of depression. In case of recurrence, further assessments were cancelled; in the other case the follow-up was continued. At 6, 12, 18, and 24 months after T0, medication use in the preceding 6 months was assessed by means of a questionnaire.

Cortisol

Participants collected their urine over a 24-h interval starting from 5:00 p.m., within 14 days after T0. The volume ranged from 460 to 5900 ml (M = 2075 ml; SD = 977). Urine samples were kept frozen at 20°C until assays were done. Cortisol was measured by radio-immunoassay (RIA) with locally prepared rabbit antiserum. It was purified on Sep-pack columns and isolated on Sephadex LH-20 columns. Cortisol scores were log-transformed.

Cognitive tasks

Participants performed two cognitive decoding tasks, one concerning the interpretation of facial expressions and the other of vocal expressions. In this study we focused on *bias* in fear perception rather than the ability to perceive fear correctly.

Task 1: perception of facial expressions

The perception of schematic facial expressions was assessed (see Fig. 1). The participants judged the 12 faces with respect to: elation, invitation, rejection, fear, anger, sadness, and disgust. Each of the emotions was rated on a 5-point scale as to their applicability to each of the 12 faces. The scale ranged from 0%–100%. The faces were presented in random order on a monitor. We distinguished 3 ambiguous faces (face 3, 4, and 5). Normal persons perceive equal amounts of positive and negative emotions from these faces (Bouhuys et al., 1995). Guided by our previous studies (see introduction), in the present study we only investigated fear perception from these ambiguous faces.

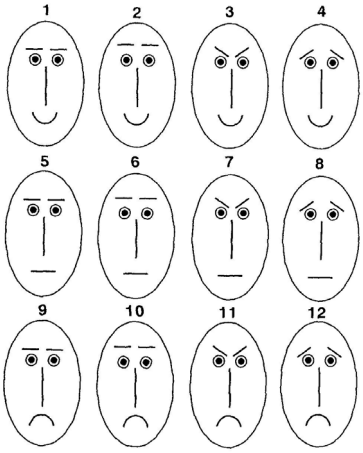

Figure 1 Faces judged by remitted subjects.

Task 2: perception of vocal expressions

The second task concerned vocal expressions and consisted of 2 subtasks, an emotion task and a control task. The control task was added to determine whether general cognitive deficits can explain results in the emotion task. This control task consisted of 18 sentences, expressed in a neutral, inquiring, or affirming tone of voice. The emotion task consisted of 36 sentences that expressed fear, sadness, anger, surprise, happiness, or were spoken in a neutral tone of voice. Speakers were 2 actors: 1 male and 1 female. Three linguistically neutral sentences were used ("the old car drives through the streets of the capital", "the large plane flies over the trees of the rainforest", and "baba baba baba"). The sentences were recorded, digitized, and implemented in a computer program. Stimuli were presented in random order via the speakers of a computer. Participants were asked to decide which of the 6 emotions was expressed in the sentences.

To assess possible perceptual bias, we counted the number of times the emotion fear was indicated when an expression was identified incorrectly. This number was adjusted for the overall number of incorrect responses (% fear perception can range from 0–100%).

Statistical analyses

Several variables can be considered as potential confounders. Age has been found to be positively associated with cortisol secretion during depression (Deuschle et al., 1998) and with emotion perception (Gunning-Dixon et al., 2003). Perception and education are assumed to be related as well. Therefore, we adjusted all analyses for gender, age, and education.

We applied Cox proportional hazards regression analyses: cortisol secretion, fear perception, and the interaction between these variables were examined with respect to the prediction of recurrence of depressive episodes. This analysis accounts for the variation in time to recurrence (i.e. the interval in weeks after T0). Observations of participants who did not experience a recurrence within the 2-year follow-up were considered censored. To explore the putative significant relation between interaction terms and recurrence of depression, partial correlations between cortisol secretion and fear perception were calculated among subjects differing in recurrence status. For between-group comparisons Fisher's z tests were applied.

In the Cox regression model two-way (gender x cortisol or gender x fear) and three-way gender interactions (gender x cortisol x fear) were tested, adjusting for lower-order terms. No significant gender interactions were found (all $p > .10$).

The variables were standardized to reduce collinearity between main effects and cross-product terms. We tested two-sidedly and alpha was set at 5%.

RESULTS

Sample characteristics and rate of recurrence

The mean BDI score at T0 was 3.6 (SD = 2.4, range 0–8). The mean HRSD score was 4.3 (SD = 3.4, range 0–15). Fifty-four (70.1%) participants used psychoactive medication at T0 (modern antidepressants, n = 42; tricyclic antidepressants, n = 11; sedatives, n = 12; mood stabilizers, n = 4). Of the 53 participants using antidepressants, 14 stopped using them in the course of the follow-up. Two participants started antidepressant medication in the course of the follow-up.

Twenty-one of the 77 participants (27.3%) experienced a new depressive episode within 2 years after T0. Of these, 12 (57.1%) were female and 9

(42.9%) were male. The majority (81.0%) of the recurrent episodes occurred within 1 year after T0.

We performed some control analyses using Cox regression. None of the demographic (gender, age, education) and clinical variables (HRSD, BDI, recurrent depression vs. single episode) nor medication use at T0 was significantly related to time to recurrence. We tested whether changes in use of antidepressant medication in the course of the follow-up were related to recurrence, by comparing participants who used antidepressants continuously (n = 39) with participants who stopped antidepressant medication (n = 14) and participants who remained free of antidepressants at all (n = 24). Time to recurrence was not significantly different for these 3 groups.

In addition, the scores on the vocal control task were not related to time to recurrence, indicating that putative deviations of vocal fear perception in participants differing in recurrence status are emotion specific.

Interrelationships between cortisol and fear perception

In the entire group the perception of vocal and facial fear was not significantly correlated (r = .161, n.s.). This was also true for the relationship between cortisol secretion and facial fear perception (r = .093, n.s.), and cortisol secretion and vocal fear perception (r = .079, n.s.).

Prediction of recurrence from cortisol or fear perception

Table 1 shows the mean levels of fear perception from ambiguous faces and vocal stimuli, together with levels of cortisol secretion, according to recurrence status.

Table 1 *Perception of fear from ambiguous faces and from vocal expressions by remitted patients with recurrence (Rec) or without recurrence of depression (Nonrec) within the following 2 years*

	Rec		Nonrec	
	M	SD	M	SD
% Facial fear	12.3	14.9	12.9	12.8
% Vocal fear	7.0	8.4	6.8	10.1
Cortisol[1]	99.7	47.2	98.9	46.0

[1]nmol/24h

Table 2, part A presents the results of the univariate Cox regression analyses, relating perception of facial and vocal fear, and cortisol to recurrence of depression. No significant main effects were found, indicating that neither levels of cortisol secretion nor levels of facial or vocal fear perception predicted recurrence of depression.

Table 2 *Cox regression analyses predicting the onset of recurrence from fear perception and cortisol secretion, adjusted for gender, age, and education*

Part A: univariate	B	HR	95% CI	p
Cortisol	-0.02	0.98	0.62–1.53	.922
% Facial fear	0.03	1.03	0.65–1.63	.907
% Vocal fear	0.05	1.05	0.68–1.63	.818
Part B: multivariate	**B**	**HR**	**95% CI**	**p**
1. Cortisol	0.18	1.20	0.71–2.04	.496
% Facial fear	-0.27	0.77	0.42–1.38	.375
Cortisol x facial fear	0.70	2.02	1.19–3.43	**.009**
2. Cortisol	-0.01	0.99	0.62–1.56	.955
% Vocal fear	-0.16	0.86	0.51–1.43	.553
Cortisol x vocal fear	0.63	1.89	1.04–3.41	**.036**
Part C: multivariate	**B**	**HR**	**95% CI**	**p**
Cortisol	0.18	1.20	0.71–2.01	.499
% Facial fear	-0.23	0.80	0.45–1.42	.438
% Vocal fear	-0.19	0.83	0.48–1.43	.501
Cortisol x facial fear	0.67	1.95	1.18–3.22	**.009**
Cortisol x vocal fear	0.64	1.89	1.02–3.48	**.042**

Prediction of recurrence from the interaction between cortisol and fear perception

The results of the multivariate regression analyses relating cortisol secretion and the perception of facial and vocal fear to recurrence of depression are presented in Table 2, part B. We found that the interaction between cortisol

secretion and facial fear perception (part B1) as well as the interaction between cortisol secretion and vocal fear perception (part B2) predicted recurrence of depression significantly. Figure 2 illustrates these interaction effects by depicting the percentage of recurrence in subgroups, differing in levels of cortisol secretion and fear perception (split half: high vs. low). The figure shows that remitted patients who had high levels of cortisol secretion and high levels of fear perception (either facial or vocal) were at substantially higher risk of becoming depressed again. Moreover, remitted patients with low levels of cortisol secretion and low levels of fear perception were at higher risk to experience recurrence as well.

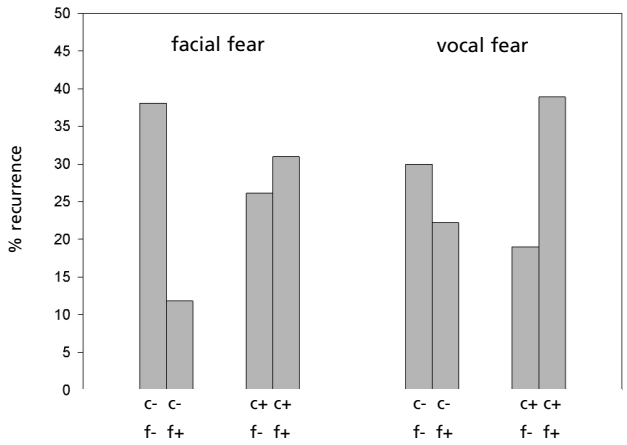

Figure 2 Percentage of recurrence in remitted patients differing in 24-h cortisol secretion (high: c+ and low: c-) and facial and vocal fear perception (high: f+ and low: f-).

The association between cortisol secretion and fear perception in the recurrent and the nonrecurrent groups, as depicted in Figure 3, helps to understand these significant interaction effects. The partial correlations between cortisol secretion and facial fear perception were in the recurrent group: r = .511 (p =. 030) and in the nonrecurrent group r = -.121 (p = .390). These correlation coefficients differed significantly from each other (Fisher's z test: p = .014). Hence, only for participants with a recurrent episode a significant association existed between cortisol secretion and facial fear

perception. A similar trend was found for the perception of fear from vocal expressions: the relationships between cortisol secretion and vocal fear perception were in the recurrent group r = .444 (p = .065) and in the nonrecurrent group r = -.031 (p = .823). The latter correlation coefficients tended to differ from each other (Fisher's z test: p = .067).

These results support our hypothesis that the association between cortisol secretion and fear perception sets persons at risk for depression recurrence.

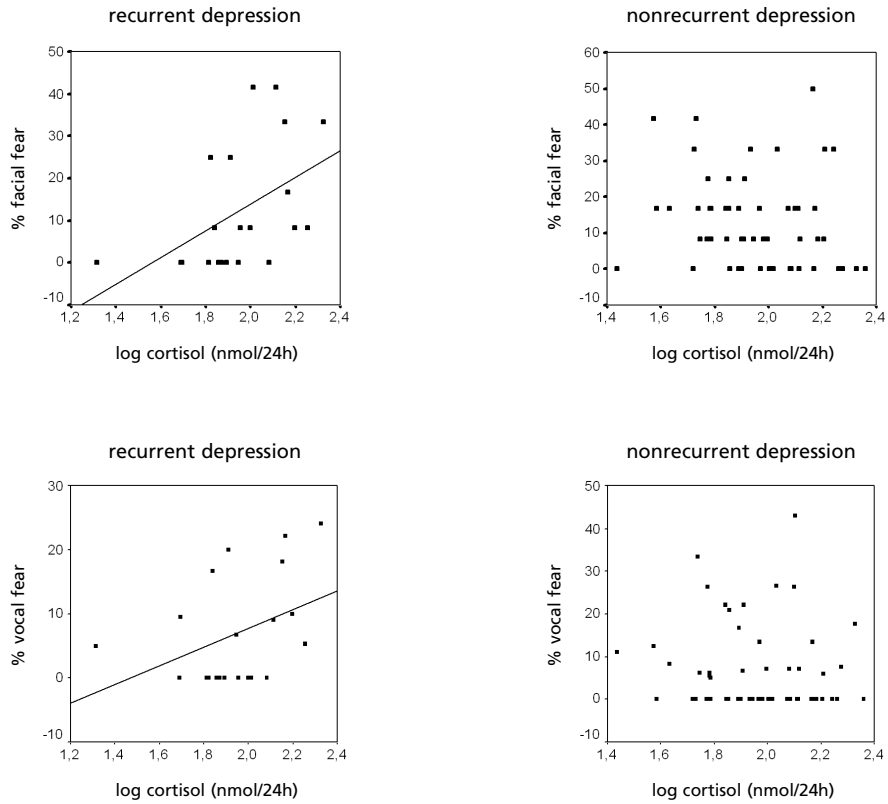

Figure 3 Association between 24-h cortisol secretion and perception of facial and vocal fear.

Additional analysis

We asked the question whether risk of recurrence connected to the one type of fear perception could be explained by the other type. A positive answer is not very likely as no direct relationship existed between the two types of fear perception. Indeed, Table 2, part C shows that both interaction terms contribute significantly and independently to the prediction of recurrence. Therefore, we must conclude that with regard to the prediction of recurrence, facial and vocal fear perception (both in interaction with cortisol secretion) are not interchangeable, and probably refer to different aspects of fear perception.

Confounding by residual symptom severity?

To be sure that our results cannot be ascribed to "residual symptoms", we performed the above analyses (Table 2, parts A and B) including HRSD depression score as an extra covariate. All effects remained significant. Thus, our results were not confounded by residual symptom severity.

DISCUSSION

Our hypothesis that an association between cortisol secretion and perception of fear operates as a risk factor for recurrence of depression was confirmed. Patients high or low on both variables were at substantially higher risk of becoming depressed within 2 years. This increased risk was also reflected by a significant correlation between cortisol secretion and facial fear perception in subjects who experienced recurrence. A trend in the same direction was found for vocal fear perception. The baseline levels of fear perception (via either channel) and cortisol secretion per se did not predict recurrence of depression. The results cannot be explained by gender, age, general cognitive impairment, education, psychoactive medication, residual symptoms, or diagnosis (retrospectively recurrent depression vs. single episode). This is the second study that demonstrates that the association between cortisol secretion and fear perception constitutes a risk for depression (Bouhuys et al., 2005). The previous cross-sectional results are now confirmed in a prospective design.

Levels and associations

Levels of cortisol secretion or fear perception per se did not exert risk for depression recurrence. We found the same in the cross-sectional study

(Bouhuys et al., 2005). However, other studies are at variance with this result (Ribeiro et al., 1993; Zobel et al., 1999; Zobel et al., 2001; Bouhuys et al., 1999a; Bouhuys et al., 1999b). This may be explained by methodological differences. Discrepancies may be caused by lack of refinement of analysis of the HPA system (24-h cortisol secretion vs. dexamethasone/CRH challenge test) or by the fact that other emotions were studied.

It is of particular interest that the *association* between cortisol secretion and fear perception places remitted patients at risk for recurrence. This association may be an indication of an *altered organization of the stress response*. It has been theorized that in persons who are vulnerable for depression the central stress response is impaired (Holsboer, 2000). Our data suggest that such impairment may (also) be expressed in a strengthened linkage between cortisol secretion and fear perception, rather than in altered levels per se.

The fear circuit and risk of recurrence

Although we did not assess amygdalar activity, it is of interest to relate our results to evidence that suggests that amygdalar activity is related to cortisol as well as to perception of negative emotions (LeDoux, 2003; Shinnick-Gallagher et al., 2003). Many studies suggest that the amygdala is a critical neural substrate for the processing of negative threatening emotional stimuli. This neural structure seems to be particularly involved in the processing of facial stimuli (Adolphs and Tranel, 2003), although the perception of fear from vocal expressions has been implicated as well (Phillips et al., 1998). In animal and human studies it has been shown that cortisol can potentiate the processing of threatening stimuli (Van Honk et al., 2000; Shinnick-Gallagher et al., 2003). Activation of the amygdala is also associated with cognitive processes including attention and memory (Zald, 2003). Negative thoughts and a negative memory bias, which have frequently been reported for depressed persons, can in turn affect amygdalar activity.

Some authors suggest that psychopathology may develop via the process of neural sensitization or kindling. They propose that increased activity or hyperexcitability of the amygdala develops through a process of neural sensitization, in which psychological stressors initiate changes in the brain's fear circuit, leading to enhanced perception and response to subsequent threat and danger (Rosen and Schulkin, 1998). Such hypothesis is in line with the cognitive kindling hypothesis in recurrent depression (Segal et al., 1996). One may speculate that the association we found between fear perception

and cortisol secretion is the result of such a sensitization process. In other words, our data may indicate that some remitted depressed persons have developed a "sensitive fear circuit", in which cortisol and fear perception have become directly linked. Whatever the origin of this altered fear circuit, our results make plausible that these deviations in stress-adaptive mechanisms constitute a risk for recurrence of depression.

We found some support for such interpretation in a positron emission tomography (PET) study on depressed patients and controls. An association between metabolic activity of the left amygdala and cortisol secretion was found in depressed patients but not in controls (Drevets et al., 2002). Hence, these data underscore the role of the amygdala and, as in our data, suggest the emergence of specific connections (in this case between amygdalar activity and cortisol secretion), which may exert risk for recurrence of depression.

Most of the above studies are based on experimental designs and refined analyses specifically developed to demonstrate links between cortisol, amygdalar activity, and fear perception. In contrast, our 24-h urinary cortisol assessment and self-reported fear perception may be considered rather rough and global indications of stress-adaptive mechanisms. Perhaps this explains why we did not find associations between fear perception and cortisol secretion in the nonrecurrent participants. However, one may argue that it is easier to detect relationships even between these rough measures when links between fear perception and cortisol are changed and/or strengthened. Since we did find a connection between fear perception and cortisol in participants who experienced recurrence of depression, we suggest that sensitization of fear circuits may have played a role.

Facial vs. vocal expressions

The amygdala has been implicated in fear perception, whether elicited by facial or vocal expressions (Phillips et al., 1998), but visual perception seems to be more strongly related to the amygdala than auditory fear perception (Anderson and Phelps, 1998). This stronger connection for facial stimuli may explain why in the recurrent group the association between fear perception and cortisol secretion is stronger for visually than for auditory perceived fear.

We found that both interaction terms between fear perception and cortisol secretion predicted recurrence of depression independently. This finding suggests that the two channels of perception may at least be partially dependent on different brain structures (see Anderson and Phelps, 1998).

Gender differences

Different mechanisms may be involved in the etiology of depression for men and women (Weissman and Klerman, 1977; Paykel, 1991). This seems to be true for assessments on the cognitive level (Nolen-Hoeksema, 1990; Bouhuys et al., 1999a; Bouhuys et al., 2005) as well as on the neuroendocrine level (Peeters et al., 2003; Bos et al., 2005). The earlier association we found between cortisol secretion, fear perception, and recurrence was confined to women (Bouhuys et al., 2005). We could not replicate this. However, gender effects were not easy to demonstrate by means of three-way interactions, since the number of patients that developed a depressive episode was rather small (12 women and 9 men). All in all, the role of gender in mechanisms that explain recurrence of depression is far from clear and need further attention.

In sum, the present study shows that, irrespective the channel of perception (eye or ear), the association between fear perception and cortisol secretion is related to recurrence of depression. These results, now found in two different samples, need to be replicated in other institutes and need more attention in the disentanglement of the complex role of stress responses in recurrence of depression. It would be of particular interest to assess sensitivity of the fear circuit directly within individuals (in contrast to the current group-wise approach) and relate this to future depression.

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th ed.) (DSM IV)*. Washington, DC: APA.

Adolphs R and Tranel D (2003) Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologia* 41, 1281-1289.

Adolphs R (2002) Recognizing emotion from facial expressions: Psychological and neurological mechanisms. *Behavioral and Cognitive Neuroscience Reviews* 1, 21-62.

Anderson AK, Phelps EA (1998) Intact recognition of vocal expressions of fear following bilateral lesions of the human amygdala. *Neuroreport* 9, 3607-3613.

Angst J (1999) Major depression in 1998: are we providing optimal therapy? *Journal of Clinical Psychiatry 60 Supplement* 6, 5-9.

Beck AT, Ward CH, Mendelson TE, Mock JE, Erbaugh JK (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4, 561-571.

Bos EH, Bouhuys AL, Geerts E, Van Os TWDP, Van der Spoel ID, Brouwer WH, Ormel J (2005) Cognitive, physiological, and personality correlates of recurrence of depression. *Journal of Affective Disorders* 87, 221-229.

Bouhuys AL, Bloem GM, Groothuis TGG (1995) Induction of depressed and elated mood by music influences the perception of facial emotional expressions in healthy subjects. *Journal of Affective Disorders* 33, 215-226.

Bouhuys AL, Geerts E, Gordijn MC (1999a) Gender-specific mechanisms associated with outcome of depression: perception of emotions, coping and interpersonal functioning. *Psychiatry Research* 85, 247-261.

Bouhuys AL, Geerts E, Gordijn MC (1999b) Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: A longitudinal study. *Journal of Nervous and Mental Disease* 187, 595-602.

Bouhuys AL, Oldehinkel AJ, Geerts E, Flentge F, Ormel J (2005) Cortisol and fear perception are associated but only in elderly depressed women (submitted).

Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, Russell JM (2002) The impact of treatment-resistant depression on health care utilization and costs. *Journal of Clinical Psychiatry* 63, 963-971.

Deuschle M, Weber B, Colla M, Depner M, Heuser I (1998) Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: a re-evaluation study. *Stress* 2, 281-287.

Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2002) Glucose metabolism in the amygdala in depression: Relationship to diagnostic subtype and plasma cortisol levels. *Pharmacology, Biochemistry and Behavior* 71, 431-447.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48, 851-855.

George MS, Huggins T, McDermut W, Parekh PI, Rubinow D, Post RM (1998) Abnormal facial emotion recognition in depression: Serial testing in an ultra-rapid-cycling patient. *Behavior Modification* 22, 192-204.

Gotlib IH, Krasnoperova E, Yue DN, Joormann J (2004) Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology* 113, 121-135.

Gunning-Dixon FM, Gur RC, Perkins AC, Schroeder L, Turner T, Turetsky BI, Chan RM, Loughead JW, Alsop DC, Maldjian J, Gur RE (2003) Aged-related differences in brain activation during emotional face processing. *Neurobiology of Aging* 24, 285-295.

Gur RC, Erwin RJ, Gur RE, Zwil AS, Heimberg C, Kraemer HC (1992) Facial emotion discrimination: II. Behavioral findings in depression. *Psychiatry Research* 41, 241-251.

Gurguis GN, Meador-Woodruff JH, Haskett RF, Greden JF (2004) Multiplicity of depressive episodes: phenomenological and neuroendocrine correlates. *Biological Psychiatry* 27, 1156-1164.

Hale WH, Jansen JHC, Bouhuys AL, Van den Hoofdakker RH (1998) The judgment of facial expressions by depressed patients, their partners and controls. *Journal of Affective Disorders* 47, 63-70.

Hamilton M (1967) Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6, 278-296.

Hammen C (1992) Cognitive, life stress, and interpersonal approaches to a developmental psychopathology model of depression. *Development and Psychopathology* 4, 189-206.

Holsboer F (2000) The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23, 477-501.

Joiner TE, Coyne JC (1999) *The interactional nature of depression: Advances in interpersonal approaches*. Washington, DC: American Psychological Association.

LeDoux J (2003) The emotional brain, fear, and the amygdala. *Cellular and molecular Neurobiology* 23, 727-738.

Mandal MK, Bhattacharya BB (1985) Recognition of facial affect in depression. *Perceptual and Motor Skills* 61, 13-14.

Nolen-Hoeksema S (1990) *Sex differences in depression*. Stanford, CA: Stanford University Press.

Paykel ES (1991) Depression in women. *British Journal of Psychiatry* 158, 22-29.

Peeters F, Nicholson NA, Berkhof J (2003) Cortisol responses to daily events in major depressive disorder. *Psychosomatic Medicine* 65, 836-841.

Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, Williams SC, Bullmore ET, Brammer M, Gray JA (1998) Neural responses to facial and vocal expressions of fear and disgust. *Proceedings of the Royal Society of London: B. Biological Sciences* 265, 1809-1817.

Pincus HA, Pettit AR (2001) The societal costs of chronic major depression. *Journal of*

Clinical Psychiatry 62 Supplement 6, 5-9.
Ribeiro SC, Tandon R, Grunhaus L, Greden JF (1993) The DST as a predictor of outcome in depression: A meta-analysis. *American Journal of Psychiatry* 150, 1618-1629.
Rosen JB, Schulkin J (1998) From normal fear to pathological anxiety. *Psychological Review* 105, 325-350.
Rubinow DR, Post RM (1992) Impaired recognition of affect in facial expression in depressed patients. *Biological Psychiatry* 31, 947-953.
Segal ZV, Williams JM, Teasdale JD, Gemar M (1996) A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine* 26, 371-380.
Shinnick-Gallagher PE, Pitkaenen AE, Shekhar AE, Cahill LE (2003) *The amygdala in brain function: Basic and clinical approaches*. New York, NY: New York Academy of Sciences.
Van Honk J, Tuiten A, van den Hout M, Koppeschaar H, Thijssen J, de Haan E, Verbaten R (2000) Conscious and preconscious selective attention to social threat: Different neuroendocrine response patterns. *Psychoneuroendocrinology* 25, 577-591.
Weissman MM, Klerman GL (1977) Sex differences and the epidemiology of depression. *Archives of General Psychiatry* 34, 98-111.
Zald DH (2003) The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews* 41, 88-123.
Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001) Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. *Journal of Psychiatric Research* 35, 83-94.
Zobel AW, Yassouridis A, Frieboes RM, Holsboer F (1999) Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. *American Journal of Psychiatry* 156, 949-951.

5

Lack of association between conversation partners' nonverbal behavior predicts recurrence of depression, independently of personality

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ABSTRACT

High neuroticism and low extraversion are related to (recurrence of) depression. We investigated whether nonverbal involvement behavior during social interaction is one of the factors via which these relations are effectuated. We measured nonverbal expressions of involvement from videotaped behavior of remitted depressed outpatients (n = 101) and their conversation partners, and assessed self-reported neuroticism and extraversion scores. During a 2-year follow-up we assessed recurrence of depression. Twenty-eight participants (27.7%) experienced a recurrent episode. Time to recurrence was predicted by neuroticism and extraversion, and also by the degree of association between levels of nonverbal involvement behavior of conversation partners. The behavioral effect did not explain the personality effect. Neuroticism moderated the behavioral effect. The results point to the independent relevance of personality and nonverbal behavior in the long-term course of depressive disorder.

INTRODUCTION

Depressive disorder is a highly recurrent disease, with rates of relapse and recurrence as high as 20-50% within 2 years (Belsher and Costello, 1988). Identification of factors that predict recurrence is therefore of great importance. The personality factor neuroticism is one of the more reliable psychosocial predictors of recurrence thus far (Angst, 1999; Mulder, 2002). Neuroticism is a major higher order personality dimension, the core of which is a sensitivity to negative stimuli (Clark et al., 1994). Neuroticism is not only consistently related to depression (Klein et al., 2002), but in fact to all kinds of psychopathology (Clark et al., 1994), which is not surprising given its broad conceptualization. The factor therefore is only a global vulnerability marker that does not tell us anything specific about why it confers risk of depression.

Another higher-order personality dimension frequently studied in the context of depression is extraversion. Like neuroticism, extraversion is a broad personality construct, including positive emotionality, energy, affiliation, and dominance (Clark et al., 1994). It is also related to depression, but inversely. Depressives have lower levels of extraversion than controls, and low extraversion predicts a poorer course of the depression, although less consistently than high neuroticism does (Klein et al., 2002). Extraversion is more explicitly linked to overt behavior than neuroticism, theoretically as well as empirically (La France et al., 2004). Studies that relate extraversion to observations of actual behavior in the context of recurrence of depression are virtually absent. The same is true for neuroticism (see also Funder, 2001).

As we are interested in *why* high neuroticism and low extraversion increase risk of recurrence of depression, and as we presume that interpersonal behavior may play a role, in this study we relate neuroticism and extraversion to the way individuals behave in interpersonal interactions. The interpersonal realm is very important in the etiology of depression, not only because it serves as a major source of stressful experiences which may trigger depression, also because social supportive relationships can protect against depression (Joiner and Coyne, 1999). An important factor in interpersonal interaction is nonverbal communication. This factor receives strikingly little attention from clinical researchers and practitioners (Philippot et al., 2003). Nonverbal signals give significance to verbal messages and also have great communicative impact independently of speech (Depaulo and Friedman, 1998). Central to the accomplishment of satisfactory interactions are for example nonverbal

expressions of involvement (Coker and Burgoon, 1987). A number of studies found that nonverbal involvement behavior is also related to the course of depression (Zeiss and Lewinsohn, 1988; Bos et al., 2002).

Whereas the nonverbal behavior of individuals is of great importance in social interactions, the *interplay* between individuals' behavior may be so even more. Especially the extent to which interaction partners adjust their behavior to each other is interesting. Mutual adjustment of nonverbal behavior is very common in everyday interaction. It can be seen in for example posture similarity, mimicry of facial expressions, movement synchrony, and congruence of levels of behavior (Bernieri and Rosenthal, 1991; Cappella, 1996). Such mutual adjustment usually occurs unintentionally and can be observed already at a very young age. It is believed to be a fundamental aspect of human communication, serving to facilitate social intercourse and interpersonal bonding (Isabella et al., 1989; Lakin et al., 2003). This idea is corroborated by evidence that interactions characterized by a high degree of behavioral congruence and synchrony are related to feelings of rapport, affiliation, and satisfaction (Tickle-Degnen and Rosenthal, 1987; Bernieri and Rosenthal, 1991).

We expect that the degree to which interaction partners adjust their nonverbal behavior to each other is also related to the course of depression. We expect this, because satisfactory social interactions are important also in the maintenance and recurrence of depression (e.g., Joiner, 2000). Two earlier studies of our group further feed our expectation (Geerts et al., 1996; Geerts et al., 2000). These studies investigated nonverbal involvement behavior of depressed patients and their interviewers. The degree to which patients and interviewers adjusted their levels of involvement behavior to each other was predictive of improvement of the depression.

In the present study we investigate remitted outpatients and relate their personality and their nonverbal involvement behavior to recurrence of depression within 2 years. We hypothesize that the less levels of involvement behavior of participants and their conversation partners are associated, the higher the risk of recurrence is. We also expect high neuroticism and low extraversion to increase risk of recurrence. We investigate whether (any of) the risk of recurrence connected to personality can be explained by involvement behavior (mediation), or whether personality and involvement behavior influence each other in the prediction of recurrence (moderation).

METHODS

Subjects

The original sample consisted of 208 outpatients, recruited from 2 mental care centers in the northern part of the Netherlands. They were considered remitted from a depressive episode according to their practitioners. After their written informed consent the participants were screened with the Composite International Diagnostic Interview (CIDI, lifetime version; World Health Organization, 1997). Subjects were included in the study if they met DSM-IV criteria for major depressive disorder or dysthymic disorder (American Psychiatric Association, 1994). Subjects were excluded if they had a disorder with psychotic symptoms, a dysfunction of the CNS, an organic cause of the disorder, substance dependence, severe communication problems, or if the end of their last depressive episode was more than 6 months ago according to CIDI data. Subjects were also excluded if their age was lower than 18 or higher than 65 years at the day they were screened.

Remission was established with the Beck Depression Inventory (BDI; Beck et al., 1961). In accordance with the proposal by Frank et al. (1991), our remission criterion was a BDI score of 8 or less for 2 consecutive times, with a 4-week interval in between. Possibly, some participants should be classified as *recovered* according to Frank's criteria (BDI $\leq$ 8 for more than 4 months), since the end of the last depressive episode of some participants was more than 4 months ago according to CIDI data. Because BDI scores were not systematically assessed during the full length of this period, we cannot formally distinguish between remission and recovery. For that reason, we use the term *remission* for participants' state at baseline in all cases. Similarly, with regard to new depressive episodes that develop in the course of the follow-up we do not distinguish between *relapse* and *recurrence* but use the term *recurrence* throughout.

Of the original 208 participants, 35 (16.8%) were excluded from the study, 26 because they did not have the proper diagnosis, 9 because the end of their last depressive episode was more than 6 months ago. Nine participants (4.3%) preliminarily withdrew from the study. We also excluded 60 participants (28.8%) who failed to reach our remission criterion within 2 years after the screening session. The final sample consisted of 104 participants (50%).

Baseline assessments (T0)

T0 sessions consisted of a series of measurements, including interviews, self-report questionnaires, and computer tasks. The interviews took place in the beginning of the session and were videotaped for later analysis of nonverbal behavior. The first interview was the Hamilton Rating Scale for Depression (HRSD, 21-item version; Hamilton, 1967), which was assessed to get an external judgment of depressive symptom severity. This interview was also used for the behavioral analyses of the present study. The HRSD is a semi-structured interview, which means that the content of the interview is similar over all interviews, without the interaction being too much constrained. Interviewers were 3 trained research workers, 1 male and 2 female, with a mean age of 31 years (range 29–34). These were also the ones that led the participants through the other assessments. The interviewers were given no special instructions with regard to their own nonverbal displays during the interview.

After the T0 session, participants were given a booklet with self-report questionnaires to fill out at home. One of the questionnaires was the Dutch version of the Eysenck Personality Questionnaire (Revised Short Scale, EPQ-RSS; Eysenck et al., 1985), which contains 12-item subscales for neuroticism and extraversion (scores can range from 0 to 12).

Analysis of nonverbal behavior

The participant and the interviewer were seated in chairs placed approximately 1.2 m apart, half-facing each other. Two cameras were used to get a frontal view of both individuals. By means of a split-screen technique the two recordings were combined to get a synchronized view. The first 15 minutes of the videotaped HRSD interviews were used for the analysis of nonverbal behavior. Two trained scorers registered behavior of participants and interviewers by means of an event-recording system.

Different sets of behavioral elements were recorded for participants and interviewers. The choice of these specific sets of behaviors was based on a previous factor-analytic study by Bouhuys and colleagues (Bouhuys et al., 1991; Bouhuys and Van den Hoofdakker, 1991; Geerts et al., 1995). This factor analysis grouped different behavioral elements in participant vs. interviewer factors. The factor *participant involvement* consisted of gesticulations, general head movements, and gaze. The factor *interviewer involvement* consisted of yes-nodding and verbal backchannel (standardized and weighted scores, relative to speaking or listening).[1] The differences in the behavioral elements

that make up the participant and interviewer factors can be seen as a reflection of the different roles interviewers and interviewees have in a conversation.

The thus composed involvement factors proved to be predictive of the course of depression in several studies of our group (see introduction). Moreover, the factors appeared to be positively associated (Bouhuys and Van den Hoofdakker, 1991; Geerts et al., 1995) and causally related to each other (Geerts et al., 1997). The behavioral elements from which the factors are constituted are regarded as indicative of involvement in the literature as well (e.g., Cappella, 1983; Coker and Burgoon, 1987).

The two scorers each registered a different set of behavioral elements. They registered one or more of the elements in separate viewings of the videotape, depending on the difficulty to record them reliably. Frequencies and durations of the behaviors were registered, relative to a subject's speaking and listening. The mean interrater reliability (kappa) was 0.88 (range 0.68–0.96) (Cohen, 1968). The mean *intra*rater reliability was 0.90 (range 0.76–0.99).

Follow-up

BDI scores were assessed 4-weekly by mail, for up to 24 months. At 6, 12, 18, and 24 months after T0, medication use in the preceding 6 months was assessed, also by mail. If BDI scores rose above 14 for 2 consecutive times (see Frank et al., 1991), the CIDI (12-months version) was conducted to further establish recurrence of depression. In case the CIDI indicated a recurrence, further follow-up assessments were cancelled. In case the CIDI result was negative, the follow-up was continued.

[1] *Participant involvement* = 1/3look/sp + 1/3dhead/sp + 1/3dgest/sp + 1/2flook/sp + 1/2 fhead/sp + fgest/sp + dlook/li. *Interviewer involvement* = dbch/li + dyes/li + fbch/li + fyes/li (look = looking in the direction of the others face, head = general head movements, yes = yes-nodding, no = no-shaking, gest = gesticulations of all sorts, bch = verbal backchannel: "yes yes", "hmm hmm", emitted to show one is listening, d = duration, f = frequency, /sp = during speaking, /li = during listening). All behavior scores are proportional to total duration of speaking and listening, respectively. Scores are normalized over subjects. (Note: in previous studies by Bouhuys and Geerts et al. the factors were called "speaking effort" and "encouragement").

Statistical analyses

For analyses of associations between participant and interviewer involvement behavior, we used a standard correlational approach (interclass correlations). Cox proportional hazards regression analyses were used to examine the relation between predictor variables and onset of recurrent depressive episodes. Time to recurrence was defined as the interval in weeks after T0 until onset of the new depressive episode according to follow-up BDI scores. Observations of participants who did not experience a recurrence within the 2-year follow-up were considered censored. In all analyses on relations between determinants of interest and (time to) recurrence we corrected for gender, age, and education. We also corrected for the interviewer, as each of the 3 interviewers presumably had an idiosyncratic nonverbal style that may have influenced the outcome of the interaction. We investigated possible gender interactions as well, in view of the evidence in the literature of gender differences in the etiology of depression (Weissman and Klerman, 1977; Bebbington, 1998). As no significant gender interactions were found, gender interaction terms were not included in our final models.

RESULTS

Sample characteristics and rate of recurrence

The video registrations of 3 participants failed due to technical problems, leaving data of 101 participants. Of these 101 participants, 61 were female and 40 were male. Lifetime diagnosis of most subjects was major depressive disorder (n = 99). Two subjects suffered from dysthymic disorder. Seventeen subjects had "double depression". Of those having major depressive disorder, 59 had a history of recurrent depression, 40 had had a single episode. The mean age of the sample at T0 was 44.5 years (SD = 10.7, range 24–66). The mean BDI score at T0 was 3.8 (SD = 2.4, range 0–8). The mean HRSD score was 4.6 (SD = 3.2, range 0–15). The median length of the remission period preceding T0 was 11 weeks (range 4–32). Seventy-three participants (72.3%) used psychoactive medication at T0 (modern antidepressants, n = 57; tricyclic antidepressants, n = 14; sedatives, n = 16; mood stabilizers, n = 6). Of the 71 subjects using antidepressants, 20 stopped using them in the course of the follow-up. Three subjects started antidepressant medication in the course of the follow-up.

Twenty-eight of the 101 participants (27.7%) experienced a new depressive episode within 2 years after T0. Of these, 15 (53.6%) were female and 13 (46.4%) were male. The majority (75.0%) of the recurrent episodes occurred within 1 year after T0. We checked whether time to recurrence was related to the above demographic or clinical variables (Cox regression analyses). None of these variables was significantly related to time to recurrence. Neither was medication use related to time to recurrence. We tested this for each type of psychoactive medication as used at T0 (Cox regression analyses). We also investigated whether discontinuation of antidepressant medication in the course of the follow-up made a difference. We tested this by comparing subjects who used antidepressants continuously (n = 51) with subjects who stopped antidepressant medication (n = 20) and subjects who remained free of antidepressants at all (n = 27). Time to recurrence was not significantly different for these 3 groups (Cox regression analysis).

Nonverbal involvement behavior

We hypothesized that the less levels of involvement behavior of participants and interviewers are associated, the higher the risk of recurrence is. We first examined overall levels of involvement behavior, i.e. mean levels of behavior as measured over the entire interview (15 minutes). The correlation between levels of participant and interviewer involvement behavior was 0.13 in the total study group (partial correlation, n.s.). In the group that did not experience a recurrent episode in the 2-year follow-up the correlation was significantly positive (partial $r = 0.26$, $p = .032$). In the group that did experience a recurrence the correlation was negative (though not significantly so: partial $r = –0.27$, n.s.; see Figure 1). Fisher's z scores were computed to test whether the correlation coefficients in the two groups were significantly different from each other. This appeared to be the case (Fisher's $z = 2.33$, $p = .020$). Thus, the involvement behavior of participants and interviewers was indeed more congruent in dyads with nonrecurrent participants than in dyads with recurrent participants.

We subsequently investigated whether the association between the conversation partners' involvement behavior was also related to *time* to recurrence. To this end, we entered the involvement factors and their interaction term in a Cox regression model. The involvement factors themselves were not related to time to recurrence, but the interaction between the two factors was (HR = 0.20, CI = 0.05–0.79, $p = .022$). To visualize this interaction effect, we divided

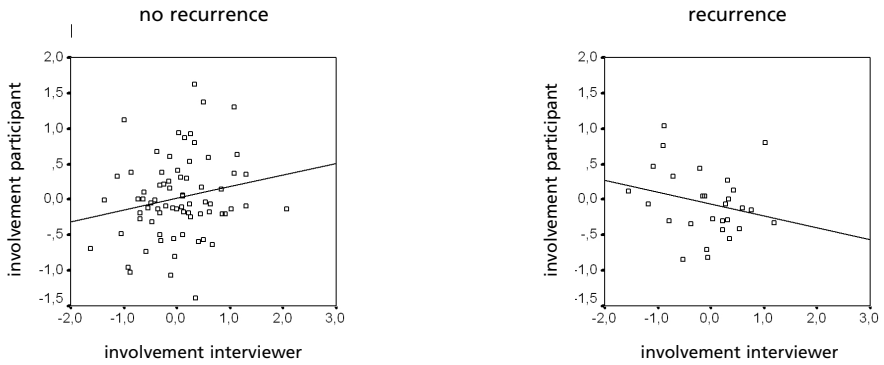

Figure 1 Correlation between levels of involvement behavior of participants and interviewers for dyads with participants that did not experience a recurrence (left panel) and dyads with participants that did experience a recurrence (right panel).

the participant and the interviewer involvement factors into lower and higher halves (median splits) and plotted the estimated survival curves for the 4 different possible combinations of levels of involvement behavior (low-low, low-high, high-low, high-high; see Figure 2). The figure shows that recurrence rates were relatively low when the participant and the interviewer showed congruent levels of involvement behavior (i.e. both low or both high). In a different way, we see here again that when levels of behavior of participants and interviewers were more associated, the risk of recurrence was lower.

Personality and involvement behavior

Personality data were missing for 1 recurrent participant, so the number of participants for analyses with personality variables is 100 (27 recurrent). The mean neuroticism score of the sample was 6.5 (SD = 3.3, range = 0–12). The mean extraversion score was 6.9 (SD = 3.8, range 0–12). We investigated the relation between personality and time to recurrence and the possible mediating effects of nonverbal involvement behavior in a hierarchical multivariate Cox regression model. Table 1 presents the results. After adjustment for our confounders, we introduced extraversion into the model as the first determinant. As can be seen from the table, extraversion was significantly predictive of time to recurrence. The hazard ratio was 0.90, indicating that a 1-point increase in extraversion decreases the hazard of recurrence with 10%. In the

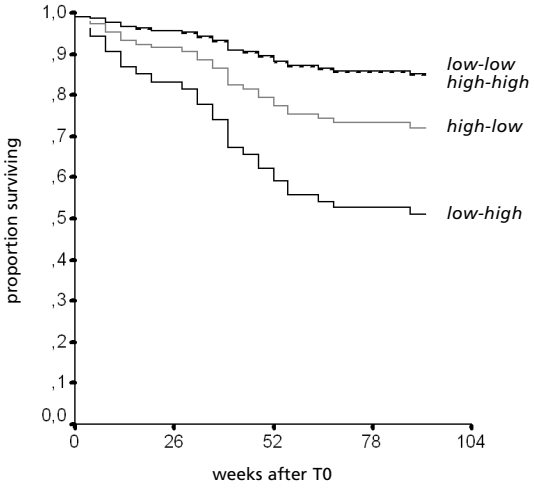

Figure 2 Survival functions for 4 different groups representing 4 different combinations of levels of nonverbal involvement behavior within dyads: low-low = participant and interviewer involvement low (n = 24); high-high = participant and interviewer involvement high (n = 25); high-low = participant involvement high, interviewer involvement low (n = 26); low-high = participant involvement low, interviewer involvement high (n = 26).

second step, we added neuroticism to the model. Neuroticism also significantly predicted time to recurrence. The hazard ratio was 1.17, indicating that a 1-point increase in neuroticism increases the hazard of recurrence with 17%. Due to the neuroticism effect, the extraversion effect was not significant anymore. When extraversion was not controlled for, the neuroticism effect was somewhat stronger (univariate test, not shown in the table, HR = 0.20, CI = 1.05–1.37, p = .009). Thus, our expectation that high neuroticism and low extraversion increase risk of recurrence was confirmed, and high neuroticism appeared the strongest risk factor.

To test whether the personality effect could be (partly) explained by the involvement behavior of the conversation partners, we subsequently entered the involvement factors and their interaction term into the model (third step). The interaction between the involvement factors was significantly predictive of time to recurrence also in this multivariate model. The effect of neuroticism was not reduced by the effect of the involvement factors. Both neuroticism

and the interaction between the involvement factors remained significantly predictive of time to recurrence. Neither had the introduction of the involvement factors a substantial effect on the parameters for extraversion. We thus have no indication that the relationship between personality and recurrence is effectuated via nonverbal involvement behavior.

Table 1 *Three-step multivariate Cox regression model predicting onset of recurrence from personality and from nonverbal involvement behavior of participants and interviewers*

	B	HR	95% CI	p
1.				
Extraversion	-0.11	0.90	0.81-0.99	**.040**
2.				
Extraversion	-0.08	0.93	0.84-1.03	.164
Neuroticism	0.16	1.17	1.02-1.34	**.027**
3.				
Extraversion	-0.08	0.92	0.83-1.03	.135
Neuroticism	0.18	1.20	1.04-1.39	**.014**
Participant involvement	-0.50	0.61	0.27-1.40	.244
Interviewer involvement	0.45	1.57	0.79-3.12	.198
Participant inv. x Interviewer inv.	-1.58	0.21	0.05-0.92	**.038**

All models adjusted for gender, age, education, and interviewer; inv. = involvement.

We also tested whether personality modified the involvement interaction effect. We did this by adding a 3rd-order interaction term to the final model of Table 1, together with all 2nd-order interaction terms. We did this separately for interactions with neuroticism and extraversion. The 3rd-order interaction term with neuroticism (N x participant involvement x interviewer involvement) appeared significant (HR = 2.21, CI = 1.29–3.80, p = .004). This means that the predictive value of the involvement interaction effect was different for different levels of neuroticism. To get more insight in the nature of this interaction, we reanalyzed the above-described model, now with a categorical neuroticism variable (tertile split: low = 0–5, n = 36; medium = 6–8, n = 34; high = 9–12, n

= 30). Hazard ratios of the involvement interaction effect for different categories of neuroticism were derived by alternatively coding each of the categories 0. It appeared that the involvement interaction effect was only significant for the low and medium categories of neuroticism (HR = 0.00, p = .005, and HR = 0.04, p = .002, respectively). In participants with the highest neuroticism scores, involvement behavior was not predictive of time to recurrence (HR = 0.43, n.s.).

Temporal aspects of adjustment

Thus far, we concentrated on *overall* levels of involvement behavior, as measured over the entire interview. We disregarded the possibility that conversation partners need some time to adjust to each other. To investigate in which stage of the interview dyadic involvement behavior was predictive of recurrence, we analyzed involvement behavior over 5 consecutive fragments of 3 minutes of the interview. We tested the effect of the interaction between the involvement factors for each of these fragments separately. We found that only in the 5^{th} fragment the interaction between the involvement factors was significantly related to time to recurrence (HR = 0.30, CI = 0.11–0.83, p = .021). Thus, with respect to the prediction of recurrence from the dyads' involvement behavior, the end stage of the interaction was the most important.

Confounding by residual symptom severity?

In the above analyses, we did not adjust for baseline depression score. We did not, since participants were included in the study only when their BDI scores fell in the asymptomatic range (BDI $\leq$ 8; see Frank et al., 1991). It still may be argued that variation in residual depression score at T0 may account for some of the found effects. The HRSD scores of the subjects show greater variability than the BDI scores, and may also give a different impression of symptom severity compared to the BDI scores because the HRSD is not a self-report measure. To be sure, we performed all analyses again, now including HRSD depression score as an extra covariate. The univariate extraversion effect (Table 1, panel 1) and the multivariate neuroticism effects (Table 1, panels 2 and 3) lost their significance as a result. These effects were reduced to trends ($p < .10$). The univariate neuroticism effect remained significantly predictive of time to recurrence (p = .039). All behavioral effects remained significant as well. We conclude that our results are not confounded by residual symptom severity.

DISCUSSION

Our results on personality showed that remitted outpatients low on extraversion or high on neuroticism are at increased risk of recurrence of depression. Although this was expected given the general evidence that these factors are related to depression (Klein et al., 2002) and some earlier studies that explicitly link personality in remitted subjects to recurrence (e.g., Duggan et al., 1990; Surtees and Wainwright, 1996; Oldehinkel et al., 2003), the findings are important, as prospective studies with measurements in remission are not numerous. The finding that the prognostic effect of extraversion was outclassed by the effect of neuroticism is in line with the fact that extraversion is inversely related to neuroticism (Sanderman et al., 1995), and with the fact that neuroticism is a more consistent predictor of (recurrence of) depression than extraversion is (Klein et al., 2002).

Our behavioral results did not provide an explanation for *why* neuroticism and extraversion are related to recurrence. Lack of association between the conversation partners' involvement behavior predicted recurrence of depression, but did not mediate between personality and recurrence. In one other study that explicitly linked personality to adjustment of involvement behavior (Geerts et al., 2000), no significant correlations between personality and adjustment of behavior were found either. Possibly, neuroticism and extraversion are reflected in other nonverbal behaviors than the ones we assessed. It may also be that the risk of recurrence attached to these personality traits is not conferred by nonverbal behavior at all, and that other mechanisms are involved. Research in which personality is related to other aspects of behavior or to variables from other domains like the physiological or the cognitive is therefore needed.

Our finding that incongruence of involvement behavior during an interaction was not the result of deviant personality but predicted recurrence of depression independently, is important in its own respect. It is in line with research that stresses the significance of involvement in social interactions. Nonverbal involvement behavior is considered central to human communication (Coker and Burgoon, 1987) and has appeared especially problematic in depressives. Depressed persons often show behavioral patterns of too low or too high involvement, and both lead to interpersonal difficulties (Segrin and Abramson, 1994). Which levels of behavior are appropriate also depends on how one's interaction partners behave. Here we come to the *interaction*

aspect of social interaction. The bulk of interpersonal research of depression does not address this aspect and focuses exclusively on how the patient behaves (cf. Coyne, 1999). It neglects what happens in the interplay between patients and others, while the quality of interactions highly depends on the outcome of this interplay (Tickle-Degnen and Rosenthal, 1987; Bernieri and Rosenthal, 1991). This is substantiated by our finding that congruence of levels of involvement behavior was more important with respect to future recurrence than levels of involvement as such. Sharing levels of involvement presumably contributes to feelings of compatibility and interrelatedness in interactions, and the ability to realize this can be seen as a social skill. This ability will improve the quality of social interactions, with reduction of interpersonal stress and enhancement of social supportive resources as the likely results. This in turn decreases the risk of becoming depressed again (Joiner, 2000).

Our results corroborate and extend earlier studies of our group in which adjustment of involvement behavior in interviews with depressed patients was related to improvement of the depression (Geerts et al., 1996; Geerts et al., 2000). The present study is the first to show that adjustment of involvement behavior is also related to recurrence of depression in remitted outpatients. In the earlier studies, it was especially the time course of behavioral adjustment that was related to improvement of the depression. In line with this result, the present study showed that particularly the end stage of the interview was decisive in predicting recurrence from the dyads' involvement behavior. This suggests that conversation partners need some time to reach a balanced interaction.

In an earlier study of remitted patients (Bos et al., 2002) we did not find that adjustment of involvement behavior was related to future course. In that study, we found that low levels of involvement from the part of the patients were predictive of an unfavorable course, a finding that was not replicated in the present study. The study differed from the present one in that the sample consisted of former inpatients, the sample size was considerably smaller, and remission and relapse were less well defined and assessed (i.e. by point measurements). Moreover, the follow-up period was only 6 months. The latter is relevant as the mechanisms behind depression relapse vs. recurrence may be different (Prien et al., 1991).

An unexpected finding was that lack of adjustment of involvement behavior between interaction partners was predictive of recurrence only in

low- and medium-neurotic persons, not in high-neurotic ones. We would have expected the most neurotic persons to be the ones that would suffer most from the detrimental effects of poor nonverbal communication (or would benefit most from skillful nonverbal communication), since these persons can be considered the most sensitive to the depressogenic effects of interpersonal stress (cf. Oldehinkel et al., 2000, Kendler et al., 2004). It should be noticed that our sample as a whole had rather high neuroticism scores compared to controls (mean = 6.5, SD = 3.3; Dutch controls: mean = 4.1, SD = 3.3; Sanderman et al., 1995). Maybe, all too high levels of neuroticism overrule behavioral effects or impede the possibility to sufficiently develop compensatory behavioral skills.

A remark should be made with regard to the method we used to assess the degree of association between the conversation partners' behavior. Interclass correlations only give an impression of "relative similarity". For example, if both members of a dyad show high levels of involvement behavior, "high" means "high relative to the levels displayed by the members of other dyads". We do not know whether these levels are similar also in an absolute sense. Another issue concerns the experimental setting in which the interview took place. Clearly, this makes the interaction not an everyday one. This may have consequences for the generalizability of the results.

Although our results have to be replicated, the study points to the relevance of nonverbal aspects of interpersonal interaction in the long-term course of depressive disorder. A further step would be to investigate involvement behavior in more naturalistic interactions, especially those with significant others. These interactions in particular can be decisive in whether a remitted patient remains out of episode. Our results may also have implications for preventive treatment strategies. An important insight is that the *interplay* between patient and others is sometimes more crucial than just the patient's behavior. Behavior of people is often irreducibly intertwined, which underlines the importance of an integrative treatment approach (Coyne, 1999).

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th ed.) (DSM IV)*. Washington, DC: APA.

Angst J 1999 Major depression in 1998: are we providing optimal therapy? *Journal of Clinical Psychiatry* 60(6), 5-9.

Bebbington PE (1998) Sex and depression. *Psychological Medicine* 28, 1-8.

Beck AT, Ward CH, Mendelson TE, Mock JE, Erbaugh JK (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4, 561-571.

Belsher G, Costello CG (1988) Relapse after recovery from unipolar depression: a critical review. *Psychological Bulletin* 104, 84-96.

Bernieri FJ, Rosenthal R (1991) Interpersonal coordination: Behavior matching and interactional synchrony. In *Fundamentals of nonverbal behavior*, pp. 401-432. Eds RS Feldman and B Rime. Cambridge: Cambridge University Press.

Bos EH, Geerts E, Bouhuys AL (2002) Non-verbal interaction involvement as an indicator of prognosis in remitted depressed subjects. *Psychiatry Research* 113, 269-277.

Bouhuys AL, Jansen JHC, Van den Hoofdakker RH (1991) Analysis of observed behavior displayed by depressed patients during a clinical interview: relationships between behavioral factors and clinical concepts of activation. *Journal of Affective Disorders* 21, 79-88.

Bouhuys AL, Van den Hoofdakker RH (1991) The interrelatedness of observed behavior of depressed patients and of a psychiatrist: an ethological study on mutual influence. *Journal of Affective Disorders* 23, 63-74.

Cappella JN (1983) Conversational involvement: Approaching and avoiding others. In *Nonverbal interaction*, pp. 37-68. Eds JM Wiemann and RP Harrison. Hillsdale, NJ: Erlbaum.

Cappella JN (1996) Dynamic coordination of vocal and kinesic behavior in dyadic interaction: Methods, problems, and interpersonal outcomes. In *Dynamic patterns in communication processes*, pp. 353-386. Eds JH Watt and CA Van Lear. Thousand Oaks, CA: Sage Publications.

Clark LA, Watson D, Mineka S (1994) Temperament, personality, and the mood and anxiety disorders. Special Issue: Personality and psychopathology. *Journal of Abnormal Psychology* 103, 103-116.

Cohen J (1968) Nominal scale agreement with provision for scaled disagreement of partial credit. *Psychological Bulletin* 70, 213-220.

Coker DA, Burgoon JK (1987) The nature of conversational involvement and nonverbal encoding patterns. *Human Communication Research* 13(4), 463-494.

Coyne JC (1999) Thinking interactionally about depression: a radical restatement. In *The interactional nature of depression: advances in interpersonal approaches*, pp. 365-392. Eds TE Joiner and JC Coyne. Washington DC: American Psychological Association.

Depaulo BM, Friedman HS (1998) Nonverbal communication. In *The handbook of social psychology, Vol. 2 (4th ed.)*, pp. 3-40. Eds DT Gilbert and ST Fiske. New York, NY: McGraw-Hill.

Duggan CF, Lee AS, Murray RM (1990) Does personality predict long-term outcome in depression? *British Journal of Psychiatry* 157, 19-24.

Eysenck SBG, Eysenck HJ, Barret P (1985) A revised version of the psychoticism scale (Dutch translation: Sanderman R, Arrindell WA, Ranchor AV, Eysenck HJ, Eysenck SBG, 1995). *Personality and Individual Differences* 6, 21-29.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48, 851-855.

Funder DC (2001) Personality. *Annual Review of Psychology* 52, 197-221.

Geerts E, Bouhuys AL, Bloem GM (1997) Nonverbal support giving induces nonverbal support seeking in depressed patients. *Journal of Clinical Psychology* 53, 41-49.

Geerts E, Bouhuys AL, Meesters Y, Jansen JHC (1995) Observed behavior of patients with seasonal affective disorder and an interviewer predicts response to light treatment. *Psychiatry Research* 57, 223-230.

Geerts E, Bouhuys AL, Van den Hoofdakker RH (1996) Nonverbal attunement between depressed patients and an interviewer predicts subsequent improvement. *Journal of Affective Disorders* 40, 15-21.

Geerts E, Kouwert E, Bouhuys N, Meesters Y, Jansen J (2000) Nonverbal interpersonal attunement and extravert personality predict outcome of light treatment in seasonal affective disorder. *Journal of Affective Disorders* 59, 193-204.

Hamilton M (1967) Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6, 278-296.

Isabella RA, Belsky J, Eye A (1989) Origins of mother-infant attachment: An examination of interactional synchrony during infant's first year. *Developmental Psychology* 25, 12-21.

Joiner TE (2000) Depression's vicious scree: Self-propagating and erosive processes in depression chronicity. *Clinical Psychology: Science and Practice* 7, 203-218.

Joiner TE, Coyne JC (1999) *The interactional nature of depression: Advances in interpersonal approaches*. Washington, DC: American Psychological Association.

Kendler KS, Kuhn J, Prescott CA (2004) The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry* 161, 631-636.

Klein DN, Durbin CE, Shankman SA, Santiago NJ (2002) Depression and personality. In *Handbook of depression*, pp. 115-140. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

La France BH, Heisel AD, Beatty MJ (2004) Is there empirical evidence for a nonverbal profile of extraversion?: A meta-analysis and critique of the literature.

Communication Monographs 71, 28-48.

Lakin JL, Jefferis VE, Cheng CM, Chartrand TL (2003) The chameleon effect as social glue: Evidence for the evolutionary significance of nonconscious mimicry. *Journal of Nonverbal Behavior* 27, 145-162.

Mulder RT (2002) Personality pathology and treatment outcome in major depression: A review. *American Journal of Psychiatry* 159, 359-371.

Oldehinkel AJ, Ormel J, Neeleman J (2000) Predictors of time to remission from depression in primary care patients: Do some people benefit more from positive life change than others? *Journal of Abnormal Psychology* 109, 299-307.

Oldehinkel AJ, Van den Berg MD, Bouhuys AL, Ormel J (2003) Do depressive episodes lead to accumulation of vulnerability in the elderly? *Depression and Anxiety* 18, 67-75.

Philippot P, Feldman RS, Coats EJ (2003) The role of nonverbal behavior in clinical settings: introduction and overview. In *Nonverbal behavior in clinical settings*., pp. 3-13. Eds P Philippot, EJ Coats and RS Feldman. London: Oxford University Press.

Prien RF, Carpenter LL, Kupfer DJ (1991) The definition and operational criteria for treatment outcome of major depressive disorder. A review of the current research literature. *Archives of General Psychiatry* 48, 796-800.

Sanderman R, Arrindell WA, Ranchor AV, Eysenck HJ, Eysenck SBG (1995) *Het meten van persoonlijkheidskenmerken met de Eysenck Personality Questionnaire (EPQ). Een handleiding*. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.

Segrin C, Abramson LY (1994) Negative reactions to depressive behaviors: A communication theories analysis. *Journal of Abnormal Psychology* 103(4), 655-668.

Surtees PG, Wainwright NW (1996) Fragile states of mind: Neuroticism, vulnerability and the long-term outcome of depression. *British Journal of Psychiatry* 169, 338-347.

Tickle-Degnen L, Rosenthal R (1987) Group rapport and nonverbal behavior. In *Group processes and intergroup relations*, pp. 113-136. Ed C Hendrick. Thousand Oaks, CA: Sage Publications.

Weissman MM, Klerman GL (1977) Sex differences and the epidemiology of depression. *Archives of General Psychiatry* 34, 98-111.

World Health Organization (1997) *Composite International Diagnostic Interview (CIDI), version 2.1. Dutch translation and revision*. Amsterdam: AMC.

Zeiss AM, Lewinsohn PM (1988) Enduring deficits after remissions of depression: A test of the scar hypothesis. *Behaviour Research and Therapy* 26, 151-158.

6

Stressful life events as a link between poor nonverbal communication and recurrence of depression

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Submitted

ABSTRACT

Background
Interpersonal difficulties and stressful life events are important etiological factors in (recurrence of) depression.

Aim
To examine whether stressful life events mediate the influence of problems in nonverbal communication on recurrence of depression.

Methods
We registered nonverbal expressions of involvement from videotaped behavior of 101 remitted outpatients and their interviewers. During a 2-year follow-up, we assessed stressful life events and recurrence of depression.

Results
The less participants and interviewers had adjusted their nonverbal involvement behavior to each other, the higher the incidence of stressful life events, and –via these– the risk of recurrence of depression.

Conclusions
A poor nonverbal match during social interaction may induce stressful life events resulting in recurrence of depression. The results underline the importance of an interpersonal approach in research and treatment of recurrent depression.

INTRODUCTION

Interpersonal difficulties and lack of social support play an important role in depressive disorder (Joiner and Coyne, 1999). As a large part of interpersonal communication takes place via nonverbal channels (Depaulo and Friedman, 1998), inadequate nonverbal communication has a great share in these interpersonal problems (Segrin, 2000). An earlier study of our group showed that poor nonverbal communication also increases risk of recurrence in remitted patients (Bos et al., 2005). Especially the nonverbal *interplay* between interaction partners appeared crucial. Lack of mutual adjustment of nonverbal involvement behavior was indicative of a higher risk of recurrence.

Problems in nonverbal communication may also induce stressful life events. Stressful life events are notorious triggers of depression (Kessler, 1997; Monroe and Hadjiyannakis, 2002). Some individuals may be more prone to such events, because of the way they behave or communicate. We hypothesized that a poor nonverbal match during social interaction increases risk of recurrence (partly) because it contributes to the occurrence of stressful life events.

METHODS

Sample and design

The study sample and design has been described in detail by Bos et al. (2005). In brief, the sample consisted of 101 outpatients whose depression had remitted less than 6 months ago (non-psychotic major depressive disorder or dysthymic disorder; DSM-IV, American Psychiatric Association, 1994). The psychiatrists' diagnosis was confirmed by means of the Composite International Diagnostic Interview (CIDI, lifetime version; World Health Organization, 1997). Remission was established by means of the Beck Depression Inventory (BDI; Beck et al., 1961). The remission criterion was: a BDI score of 8 or less for 2 consecutive times, with a 4-week interval in between (see Frank et al., 1991). At baseline (T0), the Hamilton Rating Scale for Depression interview was conducted to get an external judgement of residual symptom severity (HRSD, 21-item version; Hamilton, 1967). This interview was videotaped for later analysis of nonverbal behavior. Interviewers were 3 trained research workers, 1 male and 2 female.

During the 2-year follow-up, BDI scores were assessed 4-weekly by mail. If BDI scores rose above 14 for 2 consecutive times (see Frank et al., 1991), the CIDI (12-months version) was conducted to establish recurrence of depression. In case the CIDI indicated recurrence, further follow-up assessments were cancelled. At 6, 12, 18, and 24 months after T0, and after a recurrence, stressful life events and medication use in the preceding 6 months were assessed by means of self-report questionnaires.

Stressful life events

Stressful life events were assessed by means of the Dutch version of the List of Threatening Experiences (LTE), a self-report questionnaire that examines the occurrence of stressful life events over the previous 6 months (Brugha et al., 1985). The LTE comprises 12 major categories of stressful life events. For each event, subjects can record whether it occurred and in which month. The questionnaire shows acceptable levels of reliability and validity, and comparisons with the interview-based Life Events and Difficulties Schedule (LEDS) showed that the list covers most events rated by interviewers as having a marked or moderate long-term contextual threat (Brugha and Cragg, 1990).

As we were interested in whether the occurrence of stressful life events may be influenced by the way individuals communicate with others, we divided the events into two categories: "interpersonal" and "non-interpersonal". This subdivision was largely based on the dependency/independency distinction as frequently used by other authors (e.g., Kendler et al., 1999), but besides takes into account whether interpersonal interactions may have played a role. Interpersonal events are defined as those events that may (partly) be the result of the individual's behavior in interpersonal interactions (breaking off a steady relationship; divorce; having a serious problem with a close friend, neighbor, or relative; being sacked from a job; becoming unemployed or seeking work unsuccessfully (5 items)). Non-interpersonal events are defined as those events that reasonably can be considered as not (or only very indirectly) related to the individual's behavior in interpersonal interactions (serious illness or injury; serious illness or injury happened to a close relative; death of a parent, child, or spouse; death of a close friend or relative; major financial crisis; problems with the police or court; loss of valuables (7 items)).

Nonverbal behavior

The first 15 minutes of the videotaped HRSD interview were used for the analysis of nonverbal behavior. Two trained scorers registered behavior of participants and interviewers by means of an event-recording system. The mean interrater and intrarater reliability (kappa; Cohen, 1968) were 0.88 (range 0.68–0.96) and 0.90 (range 0.76–0.99), respectively. Separate behavioral elements were recorded in separate runs of the videotape. Frequencies and durations of the behaviors were registered, relative to a subject's speaking and listening.

We focused on behavioral elements indicative of *involvement* in the interaction, as nonverbal expressions of involvement are considered central to the accomplishment of satisfactory interactions (Coker and Burgoon, 1987). Different sets of behavioral elements were recorded for participants and interviewers. The choice of these specific sets of behaviors was based on a previous factor-analytic study by Bouhuys and colleagues (Bouhuys and Van den Hoofdakker, 1991; Geerts et al., 1995), and was in line with the literature on involvement behavior (e.g., Coker and Burgoon, 1987). The factor "participant involvement" consisted of gesticulations, general head movements, and gaze. The factor "interviewer involvement" consisted of yes-nodding and verbal backchannel (see Bos et al., 2005, for the exact composition of the factors). The thus composed involvement factors have been shown to be positively associated (Bouhuys and Van den Hoofdakker, 1991) and causally related to each other (Geerts et al., 1997). A good match between the factors has been related to a favorable course of the depression (Geerts et al., 1996; Geerts, et al., 2000; Bos et al., 2005).

Statistical analysis

To examine associations between nonverbal behavior and the occurrence of stressful life events, we investigated two aspects of the life events: 1. *number of events*, i.e. the total number of stressful life events experienced during the follow-up. This measure was divided by follow-up time to adjust for individual differences in time spent in follow-up; 2. *time to event*, i.e. the time until the first stressful life event occurred. For tests on the first aspect we used linear regression analysis. For tests on the second aspect we used Cox proportional hazards regression analysis (Cox, 1972). The latter analysis yields hazard ratios with 95% confidence intervals, indicating by how much the behavioral variables raise the instantaneous probability (hazard) of a stressful life event.

Time to event was defined as the interval in weeks after T0 until the occurrence of the first stressful life event. Observations of participants who did not experience a stressful life event within the 2-year follow-up were considered censored.

Cox proportional hazards regression analysis was also used to examine associations between behavioral variables and onset of recurrent depressive episodes. In this case, hazard ratios indicate by how much the behavioral variables raise the instantaneous probability of recurrence. Time to recurrence was defined as the interval in weeks after T0 until onset of the new depressive episode according to the follow-up BDI scores. Observations of participants who did not experience a recurrence within the 2-year follow-up were considered censored.

Cox regression for time-varying covariates was used to analyze whether stressful life events predicted recurrent episodes. This approach takes into account *when* a stressful life event occurs. The occurrence of a stressful life event was binary coded and used as the time-dependent covariate. This implies that the instantaneous probability of recurrence *before* a stressful life event is compared with the probability *after* that event. Multiple events occurring within the same month were considered as one. As the events can be assumed to produce long-term threat, the time-dependent event variable was coded 1 over a 6-months period of time (the period most often used in life-events research). In case of a new event later in the follow-up, the same procedure was employed. Since empirical studies on the speed of decay of the effect of a stressful life event show considerable variation in results (e.g., Sundin and Horowitz, 2003), we also explored models in which the effect of an event was assumed to last twice as short (3 months) or twice as long (12 months).

All analyses were adjusted for gender. In analyses with behavioral variables, the interviewer was also adjusted for. Interactions with gender were investigated as well. Since no significant gender interactions were found, gender-interaction terms were removed from the final models. The level of significance was set at 0.05 (two-sided).

RESULTS

Table 1 shows the general characteristics of the study sample. Twenty-eight (28%) of the 101 participants experienced a recurrent episode within 2 years

after T0 (15 female, 13 male). The majority (75%) of these recurrences occurred during the first year. Gender, age, BDI score at T0, HRSD score at T0, and use of antidepressant medication at T0 were not significantly related to time to recurrence (Cox regression analyses). Discontinuation of antidepressant medication during the follow-up was also not related to time to recurrence (Cox regression analysis with the use of antidepressant medication as a time-dependent covariate).

Table 1 *Sample characteristics (n = 101)*

Diagnosis (DSM-IV)	
Major depressive disorder (n, %)	99 (98%)
Dysthymic disorder (n, %)	2 (2%)
Double depression (n, %)	17 (17%)
Female (n, %)	61 (60%)
Age at T0 (mean, range)	44.5 (24–66)
BDI score at T0 (mean, range)	3.8 (0–8)
HRSD score at T0 (mean, range)	4.6 (0–15)
Antidepressant medication at T0 (n, %)	71 (70%)
Discontinuation of antidepressant medication (n, %)	20 (20%)

Stressful life events

Seventy-four of the 101 participants (73%) experienced one or more stressful life events during the follow-up. Altogether, the participants reported 192 stressful life events. The mean number of events experienced during 1 year of follow-up was 1.4 (SD = 1.7, range = 0–8.7). The mean number of events of the interpersonal type was 0.5 a year (SD = 0.9, range = 0–4.3). The mean number of events of the non-interpersonal type was 0.9 a year (SD = 1.4, range = 0–8.7). Thirty-six participants (36%) experienced one or more events of the interpersonal type. Sixty-five participants (64%) had one or more events of the non-interpersonal type. Twenty-seven participants (27%) experienced both types of events.

Nonverbal behavior and the occurrence of stressful life events

We suggested that a poor nonverbal match between interaction partners contributes to the occurrence of stressful life events. We tested this hypothesis by regressing the occurrence of stressful life events during the follow-up on the nonverbal behavior of the conversation partners as measured at T0 (using the factors "participant involvement" and "interviewer involvement" and the interaction between these factors as the determinants). We first investigated the influence of nonverbal behavior on the *number of events* (total number of stressful life events adjusted for follow-up time). Not the levels of participant and interviewer involvement as such, but the interaction between the two was significantly related to the number of events (linear regression, participant involvement x interviewer involvement: ß = -0.25, t = -2.43, p = .017). This was true for events of the interpersonal type (participant involvement x interviewer involvement: ß = -0.28, t = -2.77, p = .007), but not for events of the non-interpersonal type (participant involvement x interviewer involvement: ß = -0.13, t = -1.23, p = .222). A similar pattern of results was found when we investigated the influence of nonverbal behavior on *time to event* (time after T0 until a first stressful life event occurred). The interaction between participant and interviewer involvement was particularly related to time to interpersonal events (Cox regression, participant involvement x interviewer involvement: HR = 0.17, CI = 0.05–0.54, p = .003). No relationship with time to non-interpersonal events was found (participant involvement x interviewer involvement: HR = 0.76, CI = 0.36–1.62, p = .467). Only a trend was found when all events were considered (participant involvement x interviewer involvement: HR = 0.48, CI = 0.22–1.03, p = .058). To summarize, the interaction between the levels of nonverbal involvement behavior of the conversation partners was related to both the number of stressful life events and the time of their first occurrence, and this was particularly true for events of the interpersonal type.

To get more insight in the observed interaction effects, we divided the participant and interviewer involvement factors into lower and higher halves (median splits). This yielded 4 different combinations of levels of involvement behavior within dyads (low-low, low-high, high-low, and high-high). We pooled the interviews in which the participant and the interviewer showed *congruent* levels of involvement behavior (low-low and high-high) and those in which the participant and the interviewer showed *incongruent* levels of involvement behavior (high-low and low-high). Figure 1 depicts the number of

and the time to interpersonal events, separately for these "congruent" and "incongruent" groups. As can be seen from the upper panel of the figure, the number of interpersonal events was about 3 times as high for participants of dyads with incongruent levels of involvement behavior. The lower panel of the figure shows that the hazard of experiencing an interpersonal event was

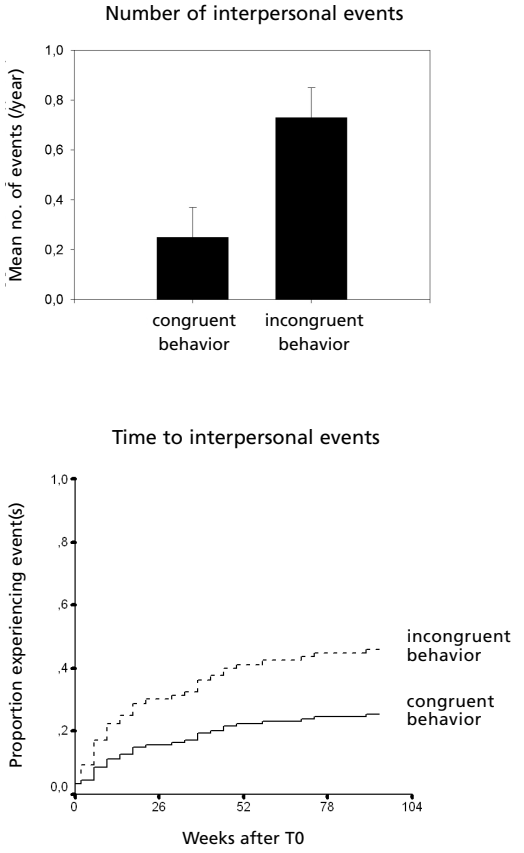

Figure 1 The occurrence of interpersonal events as a function of the incongruity of levels of nonverbal involvement behavior within dyads (n = 101). Upper panel: number of interpersonal events. Lower panel: proportion of participants experiencing one or more interpersonal events in relation to follow-up time. "Congruent behavior": participant involvement and interviewer involvement both high (or both low). "Incongruent behavior": participant involvement low and interviewer involvement high (or vice versa).

about 2 times as high for these participants. Thus, a poor nonverbal match between conversation partners was indeed related to the subsequent occurrence of stressful life events.

Stressful life events and recurrence of depression

Table 2 presents the Cox regression analyses concerning the association between stressful life events and recurrence of depression. The table shows 3 different models, one in which the effect of an event was assumed to last 6 months (our starting-point model), and two alternative models in which the effect of an event was assumed to last 3 and 12 months, respectively. As can be seen from the table, the differences between the models were small. In all 3 models stressful life events were predictive of recurrence beneath the .01 level of significance. We concluded that our choice for a 6-months model was a reasonable one and applied this model in all further analyses.

In the 6-months model, the hazard ratio connected to stressful life events was 3.29. This implies that the instantaneous probability of recurrence of depression increased 3.29-fold after the occurrence of a stressful life event. Table 3A shows the results for the different subcategories of events. Particularly events of the interpersonal type were related to recurrence of depression; interpersonal events increased the hazard of recurrence 4.57-fold. Non-interpersonal events were not significantly related to time to recurrence.

Table 2 *Cox regression analyses predicting time to recurrence on the basis of stressful life events using 3 different models of events effect decay*

Model[1]	HR	95% CI	p	-2LL
3 months	2.93	1.39–6.18	**.005**	242.2
6 months	3.29	1.51–7.17	**.003**	240.3
12 months	3.77	1.58–9.04	**.003**	239.4

[1] Effect of an event assumed to last 3, 6, and 12 months, respectively. Models adjusted for gender. HR = hazard ratio; CI = confidence interval; -2LL = -2 log-likelihood.

Nonverbal behavior and recurrence of depression

Table 3B presents our earlier finding on the association between the joint nonverbal involvement behavior of conversation partners and recurrence of depression (see Bos et al., 2005). The *interaction* between the levels of partici-

pant and interviewer involvement was significantly related to time to recurrence, not the individual levels of involvement. The nature of the interaction was such that the more congruent the levels of involvement behavior of participants and interviewers, the lower the hazard of recurrence. In other words, a poor match between the conversation partners' nonverbal involvement behavior was predictive of early recurrence.

Table 3 *Cox regression analyses predicting time to recurrence on the basis of stressful life events and nonverbal involvement behavior of participants and interviewers*

	HR	95% CI	p
A. Stressful life events[1]			
Interpersonal events	4.57	2.14–9.74	**.000**
Non-interpersonal events	1.83	0.85–3.94	.120
B. Behavior[2]			
Participant involvement	0.73	0.35–1.52	.393
Interviewer involvement	0.97	0.50–1.88	.938
Participant x interviewer involvement	0.26	0.07–0.88	**.031**
C. Behavior and interpersonal events[2]			
Interpersonal events	4.00	1.83–8.72	**.001**
Participant involvement	0.73	0.34–1.56	.418
Interviewer involvement	0.96	0.51–1.81	.892
Participant x interviewer involvement	0.39	0.11–1.42	.153
D. Behavior and non-interpersonal events[2]			
Non-interpersonal events	1.66	0.76–3.62	.201
Participant involvement	0.72	0.35–1.49	.377
Interviewer involvement	1.01	0.52–1.96	.986
Participant x interviewer involvement	0.28	0.08–0.96	**.043**

[1] Univariate analyses, adjusted for gender.
[2] Multivariate analyses, adjusted for gender and interviewer.

Mediation

We subsequently investigated whether the occurrence of stressful life events mediated the relationship between a poor nonverbal match and recurrence of depression. Therefore, we ran the model of Table 3B again, now including

stressful life events. Table 3C shows the results for the model with events of the interpersonal type. As can be seen, the interaction between participant and interviewer involvement was not significant anymore in this multivariate model. The corresponding regression coefficient was reduced by 46%. Interpersonal events were still significantly associated with time to recurrence. Thus, interpersonal events mediated part of the association between nonverbal involvement behavior and recurrence of depression.

Table 3D shows the results for the model with events of the non-interpersonal type. No mediatory effect of the stressful life events was found in this case. The interaction between participant and interviewer involvement remained significantly associated with time to recurrence, and the corresponding regression coefficient was not changed by a considerable degree (< 10%).

Part of the association between a poor nonverbal match and recurrence of depression could thus be explained by the fact that the former is related to a higher incidence of interpersonal events. Figure 2 illustrates this finding. The figure shows that recurrence was observed almost twice as often in the group of participants whose interviews were characterized by incongruent levels of involvement behavior. A relatively high proportion of these participants also

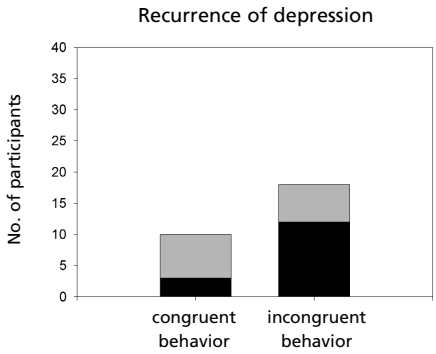

Figure 2 Recurrence of depression as a function of the incongruity of levels of nonverbal involvement behavior within dyads (n = 101). The black part of the bars denotes the number of participants who experienced both a recurrence *and* one or more interpersonal events. "Congruent behavior": participant involvement and interviewer involvement both high (or both low). "Incongruent behavior": participant involvement low and interviewer involvement high (or vice versa).

had experienced one or more interpersonal events during the follow-up (67% of the "incongruent" group, against 30% of the "congruent" group).

DISCUSSION

This study showed that problems in nonverbal communication are related to a higher subsequent exposure to stressful life events, and –via this route– to a higher risk of recurrence of depression; a poor match between the levels of nonverbal involvement behavior of remitted depressed outpatients and their conversation partners was predictive of the subsequent occurrence of stressful life events, particularly of events that were interpersonal in nature. Stressful life events in turn were predictive of recurrence of depression.

Poor nonverbal communication contributes to the occurrence of stressful life events

Our results support the notion that stressful life events do not always occur at random but may arise from the individual's own behavior. Thus far, this notion particularly found support from studies showing that certain personality dimensions like neuroticism are related to a higher exposure to stressful events (e.g., Ormel and Wohlfarth, 1991; Van Os et al., 2001). The value of the present study is that we related event exposure to what individuals actually *do*. Our measure consisted of direct observations of the individual's behavior during a conversation. Such measure does not suffer from the subjectivity that is inherent to the self-report questionnaire, the tool most often used in life-events research. Moreover, in contrast to a neuroticism score, behavioral assessments may provide information about *why* some individuals generate more stressful life events than others do.

We focused on the individual's behavior during interpersonal interaction. Interpersonal stress is an important risk factor in depression, and social support is an important protective factor (Joiner and Coyne, 1999). Our study showed that especially the result of the *interplay* between interaction partners' behavior was indicative of the subsequent occurrence of stressful life events. When levels of nonverbal involvement behavior of participants and interviewers were well adjusted to each other, the participant less frequently encountered a stressful life event during the follow-up. A good nonverbal match between interaction partners thus may avert stressful events. Such is

well conceivable in the light of some central elements of human communication theory. First, nonverbal behavior is very important in interpersonal communication, at least as important as the spoken word (Depaulo and Friedman, 1998). Secondly, mutual adjustment of nonverbal behavior is a very common aspect of normal human interaction. It can be seen in, for example, posture mirroring, facial mimicry, movement synchrony, and congruence of mean levels of behavior, and is related to feelings of mutual affiliation, rapport, and satisfaction (Tickle-Degnen and Rosenthal, 1987; Bernieri and Rosenthal, 1991). Whereas mutual adjustment of nonverbal behavior of interaction partners contributes to the success of an interaction, interactions likely become inconvenient and stressful when interaction partners do not "get it together". Eventually this may culminate in stressful life events as the ones reported in the present study. That we found this to be the case exclusively for events of the interpersonal type makes the result even more convincing, since these events were defined as those that may result from the individual's behavior during interpersonal interactions.

Stressful life events predict recurrence of depression

Our finding that stressful life events increase risk of recurrence of depression is not new, but nevertheless important. Most evidence on the depressogenic effect of stressful life events concerns first onsets of depression. Studies that specifically focus on recurrence in remitted patients are scarce (Monroe and Hadjiyannakis, 2002). Such studies are relevant since the role of stressful life events (and the role of the patient as a potential stress generator) may change over time with recurrences of the disease (Harkness et al., 1999; Kendler et al., 2000; Ormel et al., 2001). Our study besides had the advantage of a prospective design, and remission as well as recurrence were well defined and established.

We found that stressful life events of the interpersonal type were more potent predictors of recurrence than events of the non-interpersonal type were. One explanation for this finding is that interpersonal events were more likely a consequence of the individual's own behavior (as this was implicated in the definition). Therefore, these events may more easily give rise to feelings of guilt, incompetence, and reduced self-esteem. Such feelings may in turn contribute to the development of depressive symptomatology (Roberts and Monroe, 1999). This explanation is in line with general evidence that events which may have resulted from the individual's own behavior ("dependent"

events) are more strongly associated with subsequent depression than "independent" events are (e.g., Kendler et al., 1999).

One may dispute the validity of our subcategories of stressful life events. Some events categorized as "interpersonal" could in fact have occurred independently of the individual's behavior in interpersonal interactions, while some "non-interpersonal" events could have been an (indirect) result of it. We agree. We categorized the events according to the *likelihood* that they are influenced by the individual's interpersonal behavior. Thus, the distinction between our categories is a gradual one and not based on the participants' information. This is a drawback inherent in the use of a simple questionnaire. We nevertheless feel confident about the findings, since nonverbal behavior was related to stressful life events also when we did not subdivide the events.

Stressful life events mediate between poor nonverbal communication and recurrence of depression

Our earlier finding that a poor nonverbal match between remitted patients and their interviewers is indicative of increased risk of recurrence has not been an isolated one. Our research group showed that lack of mutual adjustment of nonverbal behavior also impedes improvement of the depression in depressed patients (Geerts et al., 1996; Geerts et al., 2000). We thus far interpreted these findings by reference to the relevance of well-adjusted nonverbal behavior to the success of interpersonal interactions (see above), and the importance of inadequate interpersonal interactions and lack of social support in the etiology of depressive disorder (e.g., Joiner and Coyne, 1999). We assumed that dysfunctional interpersonal skills, such as the inability to get at the same nonverbal "wavelength" with one's interaction partners, increase risk of depression because they increase the likelihood that interpersonal interactions become problematic and stressful. We now have evidence that this is the case. We found that stressful interpersonal events mediated part of the relationship between poorly adjusted nonverbal behavior and recurrence of depression. Thus, a poor nonverbal match during social interaction increases risk of depression (partly) *via* its contribution to the occurrence of stressful life events.

CLINICAL IMPLICATIONS

- A good nonverbal match during social interactions can protect against recurrence of depression by preventing stressful life events.
- The occurrence of stressful life events depends in part on the remitted patient's own behavior during social interactions.
- Particularly what happens in the interplay between patients and others is important.

LIMITATIONS

- Nonverbal behavior was measured in an experimental setting, which may not be representative for everyday social interaction.
- The degree of congruence between levels of involvement behavior within dyads could be determined only with reference to the levels of involvement behavior as displayed by other dyads.
- The assessment of stressful life events was restricted to a simple self-report questionnaire.

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th ed.) (DSM IV)*. Washington, DC: APA.

Beck AT, Ward CH, Mendelson TE, Mock JE , Erbaugh JK (1961) An inventory for measuring depression. *Archives of General Psychiatry* 4, 561-571.

Bernieri FJ, Rosenthal R (1991) Interpersonal coordination: Behavior matching and interactional synchrony. In *Fundamentals of nonverbal behavior*, pp. 401-432. Eds RS Feldman and B Rime. Cambridge: Cambridge University Press.

Bos EH, Bouhuys AL, Geerts E, Van Os TWDP, Ormel J (2005) Lack of association between conversation partners' nonverbal behavior predicts recurrence of depression, independently of personality. *Psychiatry Research* (in press).

Bouhuys AL, Van den Hoofdakker RH (1991) The interrelatedness of observed behavior of depressed patients and of a psychiatrist: an ethological study on mutual influence. *Journal of Affective Disorders* 23, 63-74.

Brugha T, Bebbington P, Tennant C, Hurry J (1985) The list of threatening experiences: a subset of 12 event categories with considerable long-term contextual threat. (Dutch translation and revision: H Kluiter, A Smit, BG Tiemens). *Psychological Medicine* 15, 189-194.

Brugha TS, Cragg D (1990) The list of threatening experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica* 82, 77-81.

Cohen J (1968) Nominal scale agreement with provision for scaled disagreement of partial credit. *Psychological Bulletin* 70, 213-220.

Coker DA, Burgoon JK (1987) The nature of conversational involvement and nonverbal encoding patterns. *Human Communication Research* 13(4), 463-494.

Cox DR (1972) Regression models and life tables. *Journal of the Royal Statistical Society* 34, 187-220.

Depaulo BM, Friedman HS (1998) Nonverbal communication. In *The handbook of social psychology, Vol. 2 (4th ed.)*, pp. 3-40. Eds DT Gilbert and ST Fiske. New York, NY: McGraw-Hill.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM 1991 Conceptualization and rationale for consensus definitions of terms in major depressive disorder. *Archives of General Psychiatry* 48, 851-855.

Geerts E, Bouhuys AL, Bloem GM (1997) Nonverbal support giving induces nonverbal support seeking in depressed patients. *Journal of Clinical Psychology* 53, 41-49.

Geerts E, Bouhuys AL, Meesters Y, Jansen JHC (1995) Observed behavior of patients with seasonal affective disorder and an interviewer predicts response to light treatment. *Psychiatry Research* 57, 223-230.

Geerts E, Bouhuys AL, Van den Hoofdakker RH (1996) Nonverbal attunement between depressed patients and an interviewer predicts subsequent improvement. *Journal of*

Affective Disorders 40, 15-21.
Geerts E, Kouwert E, Bouhuys N, Meesters Y, Jansen J (2000) Nonverbal interpersonal attunement and extravert personality predict outcome of light treatment in seasonal affective disorder. *Journal of Affective Disorders* 59, 193-204.
Hamilton M (1967) Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* 6, 278-296.
Harkness KL, Monroe SM, Simons AD, Thase M (1999) The generation of life events in recurrent and non-recurrent depression. *Psychological Medicine* 29, 135-144.
Joiner TE, Coyne JC (1999) *The interactional nature of depression: Advances in interpersonal approaches*. Washington, DC: American Psychological Association.
Kendler KS, Karkowski LM, Prescott CA (1999) Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry* 156, 837-841.
Kendler KS, Thornton LM, Gardner CO (2000) Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *American Journal of Psychiatry* 157, 1243-1251.
Kessler RC (1997) The effects of stressful life events on depression. *Annual Review of Psychology* 48, 191-214.
Monroe SM, Hadjiyannakis K (2002) The social environment and depression. Focusing on severe life stress. In *Handbook of depression*, pp. 314-340. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.
Ormel J, Oldehinkel AJ, Brilman EI (2001) The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry* 158, 885-891.
Ormel J, Wohlfarth T (1991) How neuroticism, long-term difficulties, and life situation change influence psychological distress: a longitudinal model. *Journal of Personality and Social Psychology* 60(5), 744-755.
Roberts JE, Monroe SM (1999) Vulnerable self-esteem and social processes in depression: toward an interpersonal model of self-esteem regulation. In *The interactional nature of depression: Advances in interpersonal approaches*, pp. 21-35. Eds TE Joiner and JC Coyne. Washington, DC: APA.
Segrin C (2000) Social skills deficits associated with depression. *Clinical Psychology Review* 20, 379-403.
Sundin EC, Horowitz MJ (2003) Horowitz's Impact of Event Scale; evaluation of 20 years of use. *Psychosomatic Medicine* 65, 870-876.
Tickle-Degnen L, Rosenthal R (1987) Group rapport and nonverbal behavior. In *Group processes and intergroup relations*, pp. 113-136. Ed C Hendrick. Thousand Oaks, CA: Sage Publications.
Van Os J, Park SB, Jones PB (2001) Neuroticism, life events and mental health: evidence

for person-environment correlation. *British Journal of Psychiatry Supplement* 40, 72-77.
World Health Organization (1997) *Composite International Diagnostic Interview (CIDI), version 2.1. Dutch translation and revision*. Amsterdam: AMC.

7

Integration and discussion

In this chapter, we integrate and discuss the findings of the previous chapters. We do this on the basis of the model that was presented in Chapter 1. This model describes how the various factors under investigation jointly may explain how neuroticism increases risk of recurrence of depression. In previous chapters, several parts of the model have been investigated yet. We now complete and integrate these findings in order to finally evaluate the model.

THE MODEL

We proposed that neuroticism is a concept that becomes manifest in interpersonal behavior, social cognition, and stress physiology (see Figure 1). Specifically, we proposed that high neuroticism is reflected in poor nonverbal communication, negative emotion perception, and HPA-axis hyperactivity (1). Each of these factors was thought to explain part of the risk of recurrence associated with neuroticism. Together, they were also thought to account for the fact that neurotic individuals are more prone to experience stressful life events (which further increase risk of recurrence): HPA-axis hyperactivity and negative emotion perception would mutually reinforce each other (2), negative emotion perception would lead to problems in nonverbal communication (3), and problems in nonverbal communication would contribute to the occurrence of stressful life events of the interpersonal type (4), which would trigger depression. We also expected that the effect of stressful interpersonal events would be amplified by negative emotion perception and HPA-axis hyperactivity (5).

SUMMARY OF THE FINDINGS

The most elementary parts of the model are the univariate relationships between the various factors and recurrence of depression. Most crucial in this regard was our hypothesis concerning neuroticism. The model aims at explaining *how* neuroticism increases risk of recurrence, which requires that neuroticism *does* increase risk of recurrence. In Chapter 5, we showed that this was the case. High levels of neuroticism were predictive of early recurrence. In the same chapter, we also showed that poor nonverbal communication, as measured by the degree of congruence between patients' and interviewers'

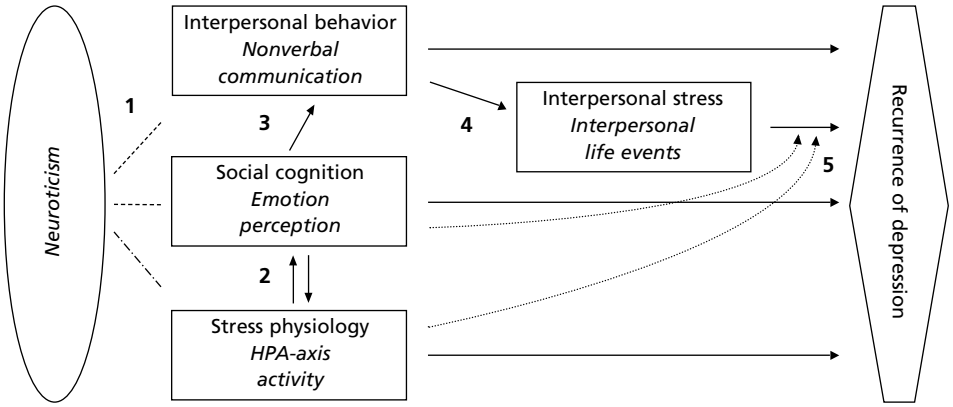

Figure 1 A multifactorial model of recurrence of depression. **1**. The personality dimension of neuroticism is reflected in poor nonverbal communication, negative emotion perception, and HPA-axis hyperactivity, each of which increases risk of depression. **2**. HPA-axis hyperactivity and negative emotion perception mutually reinforce each other. **3**. Negative emotion perception leads to poor nonverbal communication. **4**. Poor nonverbal communication contributes to the occurrence of stressful life events of the interpersonal type (which trigger depression). **5**. The effect of interpersonal events is amplified by negative emotion perception and HPA-axis hyperactivity.

nonverbal involvement behavior, was related to recurrence. The more congruent the conversation partners' nonverbal involvement behavior, the lower the risk of recurrence was. In Chapter 6, we showed that the occurrence of stressful life events also increased the risk of recurrence. This appeared to be especially true for events of the interpersonal type. Our expectations with regard to the univariate prediction of recurrence from HPA-axis hyperactivity and negative emotion perception were not confirmed. Chapter 4 showed that HPA-axis hyperactivity (as measured with 24-h urinary free cortisol levels) was not predictive of recurrence. The predictive value of negative emotion perception was investigated in the present chapter (see the Supplement at the end of this chapter). We used a summary measure of negative emotion perception (auditory + visual perception) in this case, to reduce the number of variables tested. This summary measure can be considered to represent the overall tendency to interpret emotional expressions in a negative way[1]. Contrary to

our expectations, negative emotion perception appeared not to be predictive of recurrence of depression[2].

The suggestion that neuroticism is reflected in poor nonverbal communication, negative emotion perception, and HPA-axis hyperactivity was not corroborated. In Chapter 3 we already showed that neuroticism was correlated neither to cortisol levels nor to a negative auditory perception. In the Supplement we showed that the same was true when negative auditory and negative visual perception were taken together[3]. Chapter 5 showed that neuroticism was also not reflected in poor nonverbal communication. Lack of congruence between conversation partners' nonverbal involvement behavior did not mediate any of the effect of neuroticism on recurrence of depression. Thus, neuroticism was not reflected in the behavioral, cognitive, and physiological factors we focused upon.

Our proposal that HPA-axis hyperactivity and negative emotion perception mutually reinforce each other was investigated in Chapter 4 with respect to fear perception. In the Supplement this hypothesis was investigated with respect to negative emotion perception in general[4]. The results were in support of our hypothesis. A positive association between cortisol levels and negative emotion perception was found in the subgroup of individuals who would later have a recurrence. This was also established by means of Cox regression, which showed that the interaction between cortisol and negative emotion perception was predictive of recurrence. This implied that high levels of negative emotion perception increased the risk of recurrence when cortisol levels were high as well (and the same was true when both levels were low).

Our proposal that negative emotion perception leads to poor nonverbal communication was tested in the Supplement and not confirmed. There was no association between negative emotion perception and the degree of congruence between patients' and interviewers' nonverbal involvement behavior[5]. Also the expectation that the effect of stressful interpersonal events is amplified by negative emotion perception and HPA-axis hyperactivity was not corroborated (Supplement). There was no significant interaction between these factors and interpersonal events in the prediction of recurrence[6].

The hypothesis that poor nonverbal communication contributes to the occurrence of stressful interpersonal events (which subsequently trigger depression) was confirmed. In Chapter 6 we showed that lack of congruence between conversation partners' nonverbal involvement behavior was related

to the subsequent occurrence of stressful life events, especially to those of the interpersonal type. These interpersonal events partly mediated the effect of lack of nonverbal congruence on recurrence of depression. Thus, poor nonverbal communication indeed increased risk of recurrence partly via its contribution to the occurrence of stressful interpersonal events.

Less directly relevant to our model, but relevant to the interpretation of the findings, are the results of Chapter 3. This chapter showed that individuals with a *history* of recurrent depression differed from individuals with only a single previous episode of depression, as regards HPA-axis activity and emotion perception. A history of recurrence was related to higher levels of cortisol. Women with a history of recurrent depression also had a more negative auditory perception than women with a single previous episode. The latter could also be found when negative auditory and negative visual perception were taken together (results not presented). Neuroticism scores were not significantly higher in individuals with a history of recurrent depression.

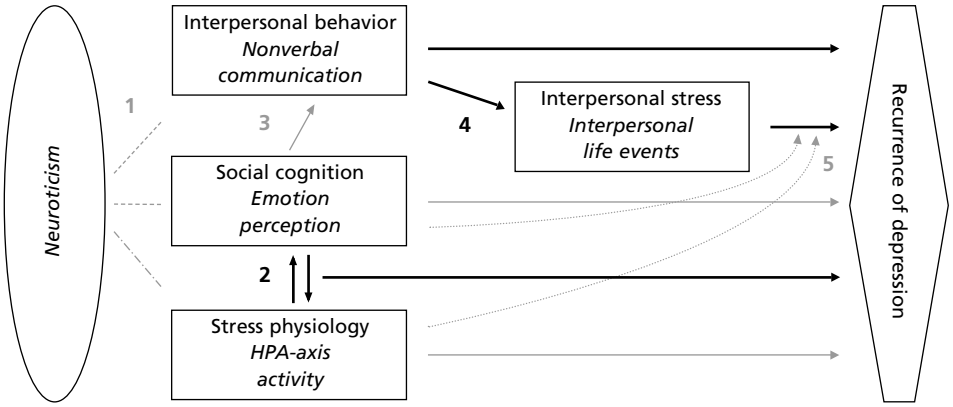

Figure 2 Summary of results. Shadow lines represent hypotheses that were not confirmed.

DISCUSSION

Some parts of the model were corroborated, other parts were not. In this section we set these findings in perspective.

Univariate prediction of recurrence

Our hypotheses on the univariate prediction of recurrence were only partly confirmed. High neuroticism levels, poor nonverbal communication (i.e. lack of congruence between conversation partners' nonverbal involvement behavior), and stressful life events (especially events of the interpersonal type) increased the risk of recurrence of depression. High cortisol levels and negative emotion perception were only related to subsequent depression in interaction with each other. Below, some relevant considerations regarding these univariate effects (or lack of effects).

Neuroticism

The personality dimension of neuroticism has been very consistently associated with depression, but the question of whether it is not merely a concomitant of the disease is still a matter of dispute. Neuroticism waxes and wanes when the depression comes and goes. Moreover, some authors have reported that neuroticism scores of remitted depressives do not differ from population norms (see Ch 1, section 2.1). These findings have led to the suggestion that high neuroticism is only a state effect of the depression (Barnett and Gotlib, 1988; Clark et al., 1994). Part of the negative findings of studies comparing remitted samples with population samples, however, may be due to selection effects. As neuroticism is associated with a poorer course, samples of remitted depressives may include a disproportionate number of individuals low on neuroticism (Klein et al., 2002). On the other hand, population samples may include a fair number of high neurotic individuals, as neuroticism (like depression) is rather common in the general population (Barnett and Gotlib, 1988). The neuroticism scores of the sample of remitted individuals investigated in the present study seemed to be well beyond those of norm scores (see Ch 5). More importantly, they were also predictive of subsequent recurrence. This finding is important, as other studies that have prospectively related neuroticism to recurrence of depression often assessed neuroticism only during the depression, or they did not use a proper remission criterion when they measured neuroticism in remission (Klein et al., 2002; Mulder,

2002). The latter is important because it reduces the possibility that one is merely measuring residual depressive symptoms, which themselves are related to a higher chance of relapse (Paykel et al., 1995). In our study, remission was well defined and established, and the few residual symptoms that may have remained were statistically controlled for. Thus, we are confident that it was not merely residual depression that we measured with the neuroticism scores.

Nonverbal communication

Our finding that recurrence of depression could be predicted from the degree of congruence between conversation partners' nonverbal involvement behavior can be considered the most extraordinary finding of the present study. Although this finding fits in with existing evidence and theories from human communication research (see Ch 1, section 2.3), it is extraordinary because there are hardly any longitudinal studies that related observational measures of nonverbal behavior to recurrence of depression, and there are virtually no studies that related *mutual* aspects of nonverbal communication to recurrence. We showed that especially what happens in the interplay between remitted patients and others is relevant to his or her prognosis.

It can be argued that paying attention to mutual aspects of interpersonal behavior is nice, but that the remitted patient remains the principal source of the problems. This may be true and we also implicitly subscribed to such a perspective in our formulations (e.g., Ch 5 and 6). This does not mean, however, that the interplay between patients and others is not important. It may be just in this interplay that individual deficits emerge. So, while the literature shows that displaying nonverbal signals of involvement during social interaction is important (Coker and Burgoon, 1987), and the study presented in Chapter 2 led to the same conclusion, the results of the Chapters 5 and 6 showed that displaying high levels of involvement is not recommendable just like that. These results suggest that it may be more important to show *appropriate* levels of involvement. And what is appropriate depends on the behavior of the interaction partners and the context in which the interaction takes place as well.

The literature on interpersonal behavior shows that people generally match one another's patterns of nonverbal behavior, unintentionally promoting mutual feelings of bonding and affiliation, but that they show behavioral *compensation* in response to excessive proximity and intimacy (Cappella and Greene, 1982; Burgoon et al., 1993). For example, when people become very

personal in their verbal disclosures, conversation partners often respond by decreasing the level of eye contact (especially when they are strangers rather than close friends). Or imagine an unfamiliar person staring at you while standing very close to you; you will likely move away a bit. Thus, people reciprocate but also compensate each other's nonverbal signals, depending on the context of the interaction and the nature of the relationship between the interaction partners (Cappella, 1981). There is a continuous interplay between interactants in which they mutually influence each other's behavior (Cappella and Greene, 1982; Geerts et al., 1997). These processes occur largely unconsciously and usually result in an equilibrium that is comfortable for both (Cappella and Greene, 1982; Burgoon et al., 1993). When, however, one of them is not responsive to the other's signals or does not react to them appropriately, or when one of them deliberately obstructs the normal processes of mutual behavioral accommodation, the result may be a highly divergent nonverbal interaction pattern. Such interactions will likely be experienced as inconvenient and stressful. For that reason we expected that individuals who have many of such interactions would be at increased risk of recurrence. Our results indeed corroborated this expectation.

The lack of nonverbal congruence between interviewers and patients who would later have a recurrence may be ascribed to lack of behavioral adjustment from the patient's side. The interviewer, however, may also have contributed to this state of affairs. We do not mean that the interviewers would have *deliberately* refrained from adjusting their behavior (they were instructed to "do as they always do", and we statistically corrected for the interviewer in the analyses to adjust for the possibility that not all interviewers have been even socially skillful). Something in the patients' behavior, however, may have evoked such a reaction from the interviewer, and may do so as well in interactions with other people (cf. Zayas et al., 2002). The point here is that it is only in the *interplay* between these individuals and others that such problems come to the surface.

Stressful interpersonal events

Our finding that the occurrence of stressful interpersonal events was predictive of recurrence of depression was expected, but not trivial. The association between stressful life events and onset of depression has been recognized for a long time (see Ch 1). The weight of the present finding lies in the prospective way the information was gathered. Most studies done on this topic are

retrospective in nature. They compare individuals with and without a recent episode of depression on the number of life events experienced during the time before onset of this episode (usually 6 or 12 months). Thus, stressful life events are assessed *after* the onset of the depression in these studies. This is a methodological problem for various reasons (Kessler, 1997). First, the depressed state may induce a bias in recall or a differential willingness to report stressful life events (e.g., Cohen et al., 1988). Secondly, some reported events might in fact refer to the depression itself (e.g., the event assessed with the item: "I suffered a serious illness"). Thirdly, the depression may have contributed to the occurrence of some events (Hammen, 1991). The fact that "dependent" events are found to be more strongly associated with depression than "independent" events are, may partly be a consequence of this latter problem (e.g., Williamson et al., 1995).

The strength of the present study is that we assessed the occurrence of stressful life events *before* onset of the recurrent episode, throughout the follow-up, (i.e. every 6 months). In case of a recurrence, data about the months not yet investigated were gathered by an additional assessment. For the events reported on this occasion, we checked whether they occurred before onset of the depression. In case they did not, these events were discarded. In this way, the problems reported above were avoided. Thus, our measure of stressful life events was not confounded by the depression itself.

Emotion perception

Negative emotion perception was not predictive of recurrence in our study. This was not in correspondence with our expectation. This expectation, however, was based on less solid grounds than those regarding, for example, stressful life events. In Chapter 1 (section 2.2), we noted that cognitive distortions and negative biases are quite often found during depression, but far less often in remission. We also noted that evidence that such dysfunctional cognitions are causal to the depression is not unequivocal. Moreover, we pointed to the fact that it likely requires stress- or mood priming to detect dysfunctional cognitions in remitted patients or to establish the depressogenic effects of such cognitions. With respect to the studies that specifically related the decoding of vocal or facial expressions to depression, only one investigated *recurrence* of depression (Bouhuys et al., 1999). Also in this study, negative perceptual biases diminished when the depressive symptoms abated. Nevertheless, a more negative perception was related to a higher risk of

relapse. The sample size of this study was small, however, and the participants were *inpatients* tested immediately after hospital discharge. This may therefore have been a rather severe group of patients of which it was not quite sure whether they were in *stable* remission at the time of measurement.

The results of the present study add to the evidence that negative cognitive biases are not unequivocally predictive of subsequent depression. Likely, additional conditions have to be met before such biases become manifest or before they become depressogenic. For example, they may only become manifest under stressful circumstances or in a negative mood. We are not sure whether "high levels" of negative perception in our study were high also in an absolute sense. Our measure was a relative one, in the sense that we had no control group for comparison. Priming tasks might have revealed even higher levels of negative perception. These might have been found predictive of recurrence. Another possibility is that negative cognitive biases are only depressogenic in combination with other risk factors, like a hyperactive HPA axis. Our finding that high levels of negative emotion perception were predictive of recurrence when cortisol levels were high as well is suggestive in this regard. Another possibility is that negative biases mainly become manifest and/or depressogenic in case the disorder gets a recurrent course. Our finding that women with a history of recurrent depression were more negative in their perception than women with a single episode of depression can be considered as an indication for this option. We discuss these issues more extensively below (pp. 154-156).

Cortisol

With regard to cortisol, the story seems to be rather similar as the one above. High cortisol levels per se did not predict future recurrence. The evidence from the literature that they *should* is suggesting but not overwhelming (see Ch 1, section 2.4). The hypercortisolism that accompanies depression often resolves upon remission. Persistent HPA-axis hyperactivity is mainly found in patients that have suffered several recurrent episodes (Gurguis et al., 1990) or in individuals that experienced early or chronic life stress (Weinstock, 1997; Heim et al., 2002). The studies that found HPA-axis dysregulations to be predictive of subsequent recurrence all used challenge tests to assess HPA-axis hyperactivity (e.g., Targum, 1984; Charles et al., 1989; Zobel et al., 2001). These tests are a measure of the integrity of feedback inhibition of the HPA axis rather than of baseline cortisol secretion. Our measure of HPA-axis

hyperactivity, 24-h urinary free cortisol levels, was admittedly a rather rough one compared to these challenge tests. We assumed that persistent HPA-axis hyperactivity in the form of impaired feedback inhibition or hyperexcitability of the system would also be reflected in the height of 24-h cortisol levels. We expected that daily hassles would be stressful enough to activate such a hyperactive HPA axis, with enhanced or prolonged cortisol secretion as a result. Although there is concrete evidence that this is a plausible assumption (Pollard et al., 1992), it may be true only to a limited extent. Minor daily stressors may not be stressful enough to reveal a hyperactive HPA-axis in 24-h urinary free cortisol levels.

Another point is that measures of baseline cortisol levels do not make clear whether a given level of cortisol secretion is high or low *for that specific individual*. Baseline cortisol levels of healthy people show considerable variation from individual to individual (Shamim et al., 2000; Hansen et al., 2001). Hence, a "high level of cortisol" may not have been high at all for the concerning participant. An experimental challenge test would have been a more adequate instrument also in this respect. A disadvantage of experimental challenge tests, on the other hand, is that they are less naturalistic than 24-h urinary free cortisol measurements.

Thus, our measure of stress physiology may not have been sensitive enough to lay bare subtle HPA-axis dysregulations. Alternatively, it may be that more conditions have to be met before such dysregulations become depressogenic. More stress, for example. Or a concurrent negative cognitive style. Our finding that cortisol levels predicted recurrence in combination with high levels of negative emotion perception is in line with the latter idea. We return to this issue later on (pp. 154-156).

On what neuroticism is and how it increases risk of recurrence

Our proposal that neuroticism is a concept that can be substantialized by measuring interpersonal behavior, social cognition, and stress physiology was not corroborated. In remitted patients, high neuroticism was not associated with poor nonverbal communication, negative emotion perception, or high levels of cortisol. Of course, this result does not necessarily refute our suggestion. The factors we selected from these fields may not have been the right ones. Or, the way we measured them may not have been the right one. For example, the existing evidence suggests that a relationship between neuroticism and a negative bias in emotion perception can be detected especially

under stressful conditions or a negative mood (see Ch 1, section 3.1). Two previous studies of our own research group are in line with this suggestion. In a sample of healthy individuals, Bouhuys et al. studied the effect of a mood induction on the perception of emotions from facial expressions, using the same set of schematic faces as used in the present study (Bouhuys et al., 1995). They found that subjects interpreted these faces more negatively when feeling more depressed. Secondly, Geerts and Bouhuys assessed emotion perception in inpatients during the depression (Geerts and Bouhuys, 1998). They found a significant association between the level of negative emotions perceived in ambiguous faces and neuroticism scores. Moreover, this negative perception mediated the effect of neuroticism on the subsequent course of the depression. Both studies corroborate the notion that emotion perception is more negative when in a depressed mood and that a relationship between neuroticism and negative emotion perception becomes apparent especially under such circumstances. Thus again, our results may have been different when we had used a priming task to assess social cognition.

In a similar way, one could argue that another way of measuring HPA-axis hyperactivity would have led to different conclusions with regard to the relationship between neuroticism and stress physiology. For example, a more sensitive measure of HPA-axis hyperactivity, like a challenge test, might have yielded another result. Three of the 5 studies that found a positive association between high neuroticism and HPA-axis hyperactivity (see Ch 1, section 3.3) measured the cortisol response after a challenge rather than baseline cortisol (Houtman and Bakker, 1991; Kirschbaum et al, 1995; Zobel et al., 2004). There are, however, also studies that did not find a relationship between neuroticism and the cortisol response after a challenge (Roy, 1996; Schommer et al., 1999), and there is also one that reports a negative relationship (McCleery and Goodwin, 2001). This latter study has the largest sample size (n = 258). The one of Roy et al. is the only study of depressed patients; the other studies investigated healthy people. There are no studies of remitted depressed patients. All in all, there are not many studies done on this topic, results are rather inconsistent, and studies in remitted samples are lacking. Therefore, it is not sure that our results would have been different when we had used a challenge test. There is anyway a general feeling emerging from the literature that neuroticism is difficult to objectify in biological markers of disease; whereas neuroticism is strongly correlated with subjective health complaints, it is largely unrelated to objective health indicators (see Watson and

Pennebaker, 1989; Claridge and Davis, 2001). Thus, it seems hard to find the biological substrate of neuroticism.

The fact that neuroticism was not related to poor nonverbal communication is not likely a result of an insensitivity of the measure we used. At least, this measure was sensitive enough to detect differences between those who would and those who would not have a recurrent depressive episode within 2 years. More likely, neuroticism is reflected in other types of behavior than the one we measured. Which types of behavior is difficult to say; the number of studies that related neuroticism to observations of actual behavior is small and hardly any of these studies investigated behavior that is also associated with depression (see Ch 1, section 3.2). Thus, although behavior is implicated in most definitions of neuroticism, and although neuroticism is an established risk factor for depression, there are surprisingly little data on what neurotics actually *do* that increases their risk of depression. So, just like there is little evidence on how neuroticism is reflected in physiological markers of disease, to date it remains unclear how neuroticism can be objectified in behavioral phenomena.

One thing is clear; we still do not know what neuroticism is and how it increases risk of depression. One increasingly popular notion is that neuroticism *is* depression. This idea is fuelled by the observation that neuroticism scores show high correlations with depression scores, and that instruments used to assess depressive symptoms have considerable item overlap with questionnaires measuring neuroticism (Ormel et al., 2004). It does *not* seem to tally with the fact that high neuroticism is also predictive of the onset of depressive episodes, i.e. that it *precedes* the clinical manifestation of the disorder temporally. It has been suggested, however, that neuroticism is a preclinical manifestation of the disorder, or simply a reflection of an individual's characteristic level of distress (Costa and McCrae, 1980; Klein et al., 2002; Ormel et al., 2004). This way of thinking falls under the label of the "precursor model" of the relationship between personality and psychopathology, and there is considerable evidence in favor of this model (Klein et al., 2002).

However attractive and plausible this precursor model, it remains difficult to understand why neuroticism is also predictive of the development of depression when existing depressive symptoms are statistically controlled for (e.g., Ch 5). The precursor model is also difficult to reconcile with evidence that neuroticism makes individuals more sensitive to the depressogenic effects

of stressful life events (see Ch 1, section 3.4), which would rather support a vulnerability (predisposition) model. These findings suggest that there is something more to neuroticism, something that is different from depression but that does have etiological relevance to this disease. Above, we noted that neuroticism has been mainly associated with subjective complaints and that attempts to specify neuroticism in objective measures of physiology and behavior have largely failed (or have largely been absent). Possibly, neuroticism *is* mainly the tendency to experience or report subjective distress. Crudely stated: it may be mainly the tendency to fuss about things. Such is not to deny a causal role of neuroticism in depression and other kinds of pathology. Fussing about things is probably a very good means to make things worse (cf. Benson, 1997; Downey et al., 1998; Kasdan et al., 1999; Logan and Rose, 2005).

The association between HPA-axis hyperactivity and negative emotion perception

We found the expected positive association between high cortisol levels and negative emotion perception, not in the sample as a whole, but in the subgroup of participants that would later have a recurrent episode. We had reason to look at this specific subgroup. The literature shows that cortisol secretion and the perception of threatening stimuli have reciprocal effects upon each other also in healthy individuals, but these are usually short-term as they are downregulated by feedback inhibition mechanisms (see Ch 1, section 3.5). Cortisol secretion and threat perception are thought to have an excessive and prolonged influence upon each other when the neuronal pathways establishing this relationship are sensitized (a "hypersensitive fear circuit"). This would set the concerning individuals at increased risk of depression (Post and Weiss, 1998; Rosen and Schulkin, 1998; Erickson et al., 2003). Our hypothesis that HPA-axis hyperactivity and negative emotion perception mutually reinforce each other is a translation of this pathological case. We therefore expected a positive association between HPA-axis hyperactivity and negative emotion perception mainly in individuals at the highest risk of recurrence.

In a reverse way of thinking, we could also have said that the risk of recurrence is higher when HPA-axis hyperactivity and negative emotion perception amplify each other's effect. That would mean to show that the interaction between cortisol and negative emotion perception is predictive of recurrence. This appeared to be the case as well. Elaboration of this interaction effect

showed that individuals having both high levels of negative emotion perception *and* high levels of cortisol were at increased risk of recurrence. Such is more likely in case of a hypersensitive fear circuit. However, when levels of cortisol and negative emotion perception were both *low*, risk was increased as well. To understand this, we probably should not focus on the height of the levels (these are relative anyway), but rather on the fact that they are not discordant. In individuals with high values on the one factor and low values on the other, the two factors apparently do not have an excessive or prolonged effect upon each other, and therefore these individuals have a lower risk of recurrence. The low-low cases may represent individuals in which the fear circuit is sensitized but *not activated* at the time of measurement.

In Chapter 4 we specifically investigated the link between cortisol secretion and fear perception. We did so, because the literature on this topic is centered on the processing of threatening stimuli. In the present chapter, we showed that the same results were obtained when negative emotion perception in general was investigated. Possibly, all emotions with a negative valence represent a form of threat, or may be interpreted in this way. It is also plausible that the result is largely *due to* the contribution of fear perception. The fact that the interaction between cortisol and fear perception was even more strongly predictive of recurrence than the interaction between cortisol and negative emotion perception in general (HR = 2.73 and 1.80, respectively[7]), suggests that fear perception in any case plays a major role.

The results of the study presented in Chapter 3 can be seen as providing further evidence for the suggestion that individuals at increased risk of recurrence may have a hypersensitive fear circuit. First, this study showed that individuals with a history of recurrent depression have higher cortisol levels than individuals who had a single previous episode. We interpreted this finding by reference to stress-sensitization theories. Not only the experience of early or chronic stress (see Ch 1, section 2.4), but also the experience of recurrent episodes of depression is thought to bring about long-lasting changes in the neuroendocrine pathways involved in the stress response, setting these individuals at increased risk of further depression by increasing their responsivity to stress (Post, 1992; Post and Weiss, 1998). Next, the study of Chapter 3 showed that women with a history of recurrent depression also had a more negative perception than women with single episode depression. In Chapter 3, we remarked that we did not know whether the negative perception of these recurrent women reflected a pre-existing vulnerability, or

whether it represented a scar induced by previous episodes. In the present chapter we showed that negative emotion perception per se did not predict future recurrence. This would suggest that the negative perception of women with a history of recurrent depression was a scar rather than a premorbid risk factor for depression. Combining this result with the ones above, however, it seems that this scar can become a risk factor when it gets part of a hypersensitive fear circuit. Thus, if recurrent episodes leave individuals with persistent abnormalities in both the physiological stress system and the emotion perception system, and if these abnormalities get linked up with each other (i.e., the regular link between these systems becomes strengthened so that the reciprocal influences these systems have upon each other become exaggerated), increased risk of depression may be the result.

Such reasoning would fit in with the idea of "cognitive kindling". The advocates of this idea propose that the mechanism of episode sensitization as observed in the field of stress physiology also occurs in the field of cognition (Segal et al., 1996). More specifically, they postulate that the likelihood that negative patterns of information processing become activated is dependent on the frequency of their past usage. In individuals who have had several previous episodes of depression the threshold for activation of these patterns is thought to be reduced, so that activation becomes more probably in the presence of increasingly minimal cues. Possibly, the ideas of cognitive kindling and stress sensitization come together in the notion of the hypersensitive fear circuit.

All in all, it seems that negative emotion perception and HPA-axis hyperactivity do not increase risk of recurrence except when they somehow go together. This would be consonant with other recent claims that dysfunctional cognitions and hypercortisolism as such are not sufficient causes of the development of depression, but do increase risk of depression in combination with other risk factors (see Alloy et al., 1999; Cowen, 2002; Just et al., 2001; Strickland et al., 2002; Ising et al., 2005). It may also link up with common sense: having a negative view on things is not going to be a problem unless one also gets upsets of it, for example because one gets stressed very easily, has a low self-esteem, or a tendency to blame things on oneself.

The link between emotion perception and nonverbal communication

We could not establish that negative emotion perception leads to problems in nonverbal communication. With regard to this negative result, the same

explanations may hold as the ones we offered for the fact that negative emotion perception was not related to neuroticism (p. 151). So, we do not necessarily have to discard the assumption that social cognition influences interpersonal behavior, but the factors we measured from these fields may not have been the right ones, or the way we measured them may not have been the right one. The idea that social cognition affects or guides interpersonal behavior is still very plausible in view of more general evidence and theory (see Ch 1, section 3.10). Our study, however, could not materialize this idea in the sense that we did not find a relationship between a negative perception of emotional expressions and a lack of congruence between conversation partners' nonverbal involvement behavior.

The link between nonverbal communication and stressful interpersonal events

The finding that lack of nonverbal congruence during a conversation was related to the subsequent occurrence of stressful interpersonal events is an important one. It partly explained why lack of nonverbal congruence is related to recurrence of depression. Therewith, it substantiated a major presumption of the thesis, the idea that interpersonal stress plays a major role in the etiology of depression and that its occurrence may be the result of the depression-prone person's own behavior and the way other people react to this behavior. This assumption can be traced back to Coyne (see Ch 1, section 2.3). Coyne theorized that the behavior of depression-prone persons (e.g., reassurance seeking) elicits negative reactions in others which serve to exacerbate depressive symptomatology. A crucial element of this theory is the reaction of other people. Coyne suggested that these people initially may react friendly and supporting to the depression-prone person's demands, at least verbally. This person doubts their genuineness, however, especially when nonverbal signals tell a different story than verbal ones. This leads him or her again to seek for reassurance. A repetitive pattern is established in which increasing demands for reassurance are made by the depression-prone person and in which the other becomes increasingly rejecting in his (nonverbal) behavior. The other may eventually withdraw. Our finding may reflect an element of such a process. A lack of nonverbal congruence between the remitted patients and their interviewers may be a reflection of an overly demanding (or a too unresponsive) patient to which interaction partners react by showing compensatory signals. When the patient subconsciously notices

these signals but reacts inappropriately to them, for example by showing even more demanding (or even more unresponsive) behavior, a negative spiral may be initiated. The result will be a highly divergent nonverbal interaction pattern. Such interactions will usually be experienced as unpleasant or stressful, by both interaction partners. In the end, this may culminate into stressful interpersonal events.

It is plausible that disruptive interpersonal processes as the ones described above will particularly occur in *recurrent* depression. People who become depressed time and again likely get entangled in increasingly troubled interpersonal relationships (cf. Coyne, 1999). Not only because repeated episodes of depression may make former patients fearful about their ability to meet interpersonal expectations. Also because it may become increasingly difficult for the people in their environment to cope with a partner, friend, or colleague who becomes depressed over and over again. Thus, there may be something like "interpersonal kindling" as well: depression occurs in troubled interpersonal circumstances, and increasingly so when the disease gets a recurrent course.

Moderator effects

Our expectation that the depressogenic effects of stressful life events would be amplified by negative emotion perception and HPA-axis hyperactivity did not come out. It is tempting to seek a methodological explanation for these negative results as well. Our measures of HPA-axis hyperactivity and negative emotion perception might not have been sensitive enough, or the sample size might have been too small to detect interaction effects. An alternative explanation would be that these factors are no moderators of the effects of stressful life events. In discussing the literature on these topics (Ch 1) we did find evidence for the proposed modulatory effects, but this evidence was not unequivocal, and also not specific to the factors that we measured. For example, there are several indications that certain aspects of social cognition interact with stressful events, but none of these studies specifically investigated the decoding of facial or vocal expressions (Ch 1, section 3.8). In the field of stress physiology, there is only indirect evidence that HPA-axis hyperactivity increases the impact of stressful life events (Ch 1, section 3.7). Thus, possibly the factors that we investigated actually do not moderate the effects of stressful life events. Or, they do so, but only in combination with each other (cf. p. 156).

CONCLUDING REMARKS

This thesis has provided some insight in the interpersonal mechanisms underlying recurrence of depression. It has not, however, elucidated what neuroticism is and why neurotic people have a higher risk of depression. Should our model be discarded? Not necessarily. A hypothesis does not immediately have to be rejected when it is not corroborated. Hypotheses are usually embedded in broader theories and findings, and that also holds for our model. The reason why some parts of the model have not been confirmed may be that our model was wrong, but it may also be due to the methods we used, the nature of our sample, or the quirks of fate. More research should be done to decide this.

We started our investigations with the observation that depression is a highly recurrent disease, and that risk of recurrence increases with each further episode (see Ch 1, section 1). Episodes seem to beget episodes. Episodes also seem to develop more and more spontaneously with further progression of the disease. While first episodes of depression in most cases are preceded by a major stressful event, recurrent episodes appear to be triggered by increasingly minimal stress (Brilman and Ormel, 2001; Ormel et al., 2001; Monroe and Harkness, 2005). This observation suggests that the experience of a depressive episode brings about changes in affected individuals which make them more susceptible to further depression. The stress-sensitization model postulates that such changes occur in the physiological stress system, making this system hypersensitive, as a result of which minor stressors can already induce a strong stress response. The cognitive kindling model postulates that similar processes occur in cognitive systems, so that negative patterns of information processing can be activated by increasingly minimal cues. We have discussed how our results with regard to cortisol and emotion perception fit in with these ideas of physiological and cognitive kindling. We have also suggested that something similar may occur in the field of interpersonal behavior. The social relationships of people who become depressed time and again will likely become increasingly problematic and their social supportive resources more and more depleted ("interpersonal kindling").

These ideas of sensitization and kindling seem to suggest that recurrent depression is a downward spiral. This is a gloomy picture. It is not a given, however, that there is no way out. Some more optimistic perspectives will be presented in Chapter 8.

SUPPLEMENT

This supplement presents the analyses on the hypotheses not yet investigated in previous chapters. These hypotheses mainly concern emotion perception.

[1] Emotion perception was assessed with tasks on two different sensory modalities, audition and vision (the decoding of vocal and facial expressions, respectively; see Ch 3 and 4). To prevent that the analyses would suffer from capitalization of chance, we had to reduce the number of variables. We therefore constructed a summary measure of the two types of emotion perception. The idea behind this summation was that adequate emotion perception depends on the integrity of both visual and auditory channels of perception. The processing of visual and auditory cues involves separate brain mechanisms (Schroeder et al., 2003), and the current notion is that the two different sensory modalities complement each other or that their combined use makes the perceptual system more efficient (DeGelder, 2000). Thus, we reasoned that having a problem with both visual and auditory perception is presumably worse than having a problem with only one of these modalities. We therefore combined our measures of negative auditory and negative visual perception into a summary measure of negative emotion perception, which thus can be considered to represent the overall tendency to interpret emotional expressions in a negative way.

[2] Panel A of Table 1 presents the analysis on the univariate prediction of recurrence from negative emotion perception (auditory + visual). Negative emotion perception did not increase the hazard of recurrence. There was no significant interaction with gender either (HR = 1.03, CI = 0.64–1.66, n.s.). Thus, recurrence of depression could not be predicted from a tendency to interpret emotional expressions in a negative way, and this result was not different for the different sexes.

[3] To test the hypothesis that neuroticism is reflected in negative emotion perception, we calculated the correlation between neuroticism and the summary measure of negative emotion perception. This correlation was very small and not significant (partial r = 0.023, p = .827; n = 96, 26 recurrent). Thus, neuroticism was not reflected in a tendency to interpret emotional expressions in a negative way.

[4] Our proposal that HPA-axis hyperactivity and negative emotion perception mutually reinforce each other was investigated by calculating the correlation between cortisol levels and negative emotion perception, separately in the subgroup that would later have a recurrence and in the subgroup that would not have a recurrence. In the recurrent subgroup the correlation was significantly positive (partial r = 0.58, p = .012), in the nonrecurrent subgroup the correlation was not significant (partial r = -0.10, n.s.). The same result could be established by means of Cox regression (Table 1, Panel B). The interaction between cortisol and negative emotion perception was predictive of time to

recurrence. This implied that high levels of negative emotion perception increased the hazard of recurrence when cortisol levels were high as well (and the same was true when both levels were low).

Table 1 *Cox regression predicting time to recurrence*

		HR	95% CI	p
A.	Negative perception	1.01	0.79 – 1.28	.950
B.	Cortisol	1.08	0.66 – 1.78	.756
	Negative perception	1.06	0.65 – 1.73	.806
	Cortisol x negative perception	1.80	1.09 – 2.96	**.021**
C.	Negative perception	1.01	0.62 – 1.67	.955
	Interpersonal events	5.33	2.37 – 11.98	.000
	Negative perception x interpersonal events	0.90	0.39 – 2.07	.796
D.	Cortisol	1.06	0.60 – 1.89	.831
	Interpersonal events	7.72	3.16 – 18.87	.000
	Cortisol x interpersonal events	0.74	0.30 – 1.80	.500

Analyses adjusted for gender, age, and education; predictor variables are z-transformed
A: negative perception = negative auditory + negative visual emotion perception; n = 97 (27 recurrent)
B: cortisol = 24-h urinary free cortisol (log-transformed values); n = 77 (21 recurrent)
C: interpersonal events = stressful life events of the interpersonal type; n = 97 (27 recurrent)
D: n = 83 (23 recurrent)

[5] To investigate the hypothesis that negative emotion perception leads to poor nonverbal communication, we tested whether there is an association between negative emotion perception and the degree of congruence between patients' and interviewers' nonverbal involvement behavior. We did this by calculating the correlation between negative emotion perception and the interaction "patient involvement x interviewer involvement" (controlling for the main terms). This correlation was not significant (partial r = -0.09; p = .408 (n = 96, 27 recurrent). Thus, the suggestion that negative emotion perception leads to problems in nonverbal communication was not corroborated.

[6] Our proposal that the effect of stressful interpersonal events is amplified by negative emotion perception and HPA-axis hyperactivity was tested by means of Cox regression. The results are presented in Panels C and D of Table 1. Panel C shows the interaction

between negative emotion perception and interpersonal events. Panel D shows the interaction between HPA-axis hyperactivity (cortisol levels) and interpersonal events. Neither of these interactions was significantly predictive of recurrence. So, negative emotion perception and high cortisol levels did not amplify the effect of interpersonal events.

[7] We tested whether the above results would have been different when negative emotion perception was specified to fear perception. We did so, because the literature provides many indications that fear plays a special role in the etiology of depression (and other forms of psychopathology). We used a summary measure of fear perception (auditory + visual fear perception) in this case as well. The results were not very different. In all cases, levels of significance and parameter values were rather similar. Only the interaction between cortisol and fear perception was somewhat stronger (HR = 2.73, p = .001). This suggests that the significance of the interaction between cortisol and negative emotion perception (Table 1, panel B) was largely due to the contribution of fear perception.

REFERENCES

Alloy LB, Abramson LY, Whitehouse WG, Hogan ME, Tashman NA, Steinberg DL, Rose DT, Donovan P (1999) Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. *Behaviour Research and Therapy* 37, 503-531.

Barnett PA, Gotlib IH (1988) Psychosocial functioning and depression: distinguishing among antecedents, concomitants, and consequences. *Psychological Bulletin* 104, 97-126.

Benson H (1997) The nocebo effect: history and physiology. *Preventive Medicine* 26, 612-615.

Bouhuys AL, Bloem GM, Groothuis TGG (1995) Induction of depressed and elated mood by music influences the perception of facial emotional expressions in healthy subjects. *Journal of Affective Disorders* 33, 215-226.

Bouhuys AL, Geerts E, Gordijn MCM (1999) Depressed patients' perception of facial emotions in depressed and remitted state is associated with relapse: a longitudinal study. *Journal of Nervous and Mental Disease* 187, 595-602.

Brilman EI, Ormel J (2001) Life events, difficulties and onset of depressive episodes in later life. *Psychological Medicine* 31, 859-869.

Burgoon JK, Dillman L, Stern LA (1993) Adaptation in dyadic interaction: defining and operationalizing patterns of reciprocity and compensation. *Communication Theory* 3, 295-316.

Cappella JN (1981) Mutual influence in expressive behavior: adult-adult and infant-adult dyadic interaction. *Psychological Bulletin* 89, 101-132.

Cappella JN, Greene JO (1982) A discrepancy-arousal explanation of mutual influence in expressive behavior for adult and infant-adult interaction. *Communication Monographs* 49, 89-114.

Charles GA, Schittecatte M, Rush AJ, Panzer M, Wilmotte J (1989) Persistent cortisol non-suppression after clinical recovery predicts symptomatic relapse in unipolar depression. *Journal of Affective Disorders* 17, 271-278.

Claridge G, Davis C (2001) What's the use of neuroticism? *Personality and Individual Differences* 31, 383-400.

Clark LA, Watson D, Mineka S (1994) Temperament, personality, and the mood and anxiety disorders. Special Issue: Personality and psychopathology. *Journal of Abnormal Psychology* 103, 103-116.

Cohen LH, Towbes LC, Flocco R (1988) Effects of induced mood on self-reported life events and perceived and received social support. *Journal of Personality and Social Psychology* 55, 669-674.

Coker DA, Burgoon JK (1987) The nature of conversational involvement and nonverbal

encoding patterns. *Human Communication Research* 13(4), 463-494.
Costa PT, McCrae RR (1980) Influence of extraversion and neuroticism on subjective well-being: Happy and unhappy people. *Journal of Personality and Social Psychology* 38, 668-678.
Cowen PJ (2002) Cortisol, serotonin and depression: all stressed out? *British Journal of Psychiatry* 180, 99-100.
Coyne JC (1999) Thinking interactionally about depression: a radical restatement. In *The interactional nature of depression: advances in interpersonal approaches*, pp. 365-392. Eds TE Joiner and JC Coyne. Washington, DC: American Psychological Association.
DeGelder B (2000) Recognizing emotions by ear and by eye. In *Cognitive neuroscience of emotion*, pp. 62-83. Eds RD Lane and L Nadel. London: Oxford University Press.
Downey G, Freitas AL, Michaelis B, Khouri H (1998) The self-fulfilling prophecy in close relationships: rejection sensitivity and rejection by romantic partners. *Journal of Personality and Social Psychology* 75, 545-560.
Erickson K, Drevets W, Schulkin J (2003) Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience and Biobehavioral Reviews* 27, 233-246.
Geerts E, Bouhuys AL (1998) Multi-level prediction of short-term outcome of depression: the role of nonverbal interpersonal and cognitive processes and of personality traits. *Psychiatry Research* 79, 59-72.
Geerts E, Bouhuys AL, Bloem GM (1997) Nonverbal support giving induces nonverbal support seeking in depressed patients. *Journal of Clinical Psychology* 53, 41-49.
Gurguis GN, Meador-Woodruff JH, Haskett RF, Greden JF (1990) Multiplicity of depressive episodes: phenomenological and neuroendocrine correlates. *Biological Psychiatry* 27, 1156-1164.
Hammen C (1991) Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology* 100, 555-561.
Hansen AM, Garde AH, Christensen JM, Eller NH, Netterstrom B (2001) Reference intervals and variation for urinary epinephrine, norepinephrine and cortisol in healthy men and women in Denmark. *Clinical Chemistry and Laboratory Medicine* 39, 842-849.
Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB (2002) The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depression and Anxiety* 15, 117-125.
Houtman IL, Bakker FC (1991) Individual differences in reactivity to and coping with the stress of lecturing. *Journal of Psychosomatic Research* 35, 11-24.
Ising M, Lauer CJ, Holsboer F, Modell S (2005) The Munich vulnerability study on affective disorders: premorbid neuroendocrine profile of affected high-risk probands. *Journal of Psychiatric Research* 39 (1), 21-28.

Just N, Abramson LY, Alloy LB (2001) Remitted depression studies as tests of the cognitive vulnerability hypotheses of depression onset: a critique and conceptual analysis. *Clinical Psychology Review* 21, 63-83.

Kasdan ML, Lewis K, Bruner A, Johnson AL (1999) The nocebo effect: do no harm. *Journal of the Southern Orthopaedic Association* 8, 108-113.

Kessler RC (1997) The effects of stressful life events on depression. *Annual Review of Psychology* 48, 191-214.

Kirschbaum C, Prussner JC, Stone AA, Federenko I, Gaab J, Lintz D, Schommer N, Hellhammer DH (1995) Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosomatic Medicine* 57, 468-474.

Klein DN, Durbin CE, Shankman SA, Santiago NJ (2002) Depression and personality. In *Handbook of depression*, pp. 115-140. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Logan DE, Rose JB (2005) Is postoperative pain a self-fulfilling prophecy? Expectancy effects on postoperative pain and patient-controlled analgesia use among adolescent surgical patients. *Journal of Pediatric Psychology* 30, 187-196.

McCleery JM, Goodwin GM (2001) High and low neuroticism predict different cortisol responses to the combined dexamethasone/CRH test. *Biological Psychiatry* 49, 410-415.

Monroe SM, Harkness KL (2005) Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychological Review* 112, 417-445.

Mulder RT (2002) Personality pathology and treatment outcome in major depression: a review. *American Journal of Psychiatry* 159, 359-371.

Ormel J, Oldehinkel AJ, Brilman EI (2001) The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry* 158, 885-891.

Ormel J, Rosmalen J, Farmer A (2004) Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* 39, 906-912.

Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A (1995) Residual symptoms after partial remission: an important outcome in depression. *Psychological Medicine* 25, 1171-1180.

Pollard T (1992) Some determinants of population variation in cortisol levels in a British urban community. *Journal of Biosocial Science* 24, 477-485.

Post RM (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry* 149, 999-1010.

Post RM, Weiss SRB (1998) Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness

progression. *Biological Psychiatry* 44, 193-206.
Rosen JB, Schulkin J (1998) From normal fear to pathological anxiety. *Psychological Review* 105, 325-350.
Roy A (1996) HPA axis function and temperament in depression: a negative report. *Biological Psychiatry* 39, 364-366.
Schommer NC, Kudielka BM, Hellhammer DH, Kirschbaum C (1999) No evidence for a close relationship between personality traits and circadian cortisol rhythm or a single cortisol stress response. *Psychological Reports* 84, 840-842.
Schroeder CE, Smiley J, Fu KG, McGinnis T, O'Connell MN, Hackett TA (2003) Anatomical mechanisms and functional implications of multisensory convergence in early cortical processing. *International Journal of Psychophysiology* 50(1/2), 5-17.
Segal ZV, Williams JM, Teasdale JD, Gemar M (1996) A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine* 26, 371-380.
Shamim W, Yousufuddin M, Bakhai A, Coats AJ, Honour JW (2000) Gender differences in the urinary excretion rates of cortisol and androgen metabolites. *Annals of Clinical Biochemistry* 37, 770-774.
Strickland PL, Deakin JF, Percival C, Dixon J, Gater RA, Goldberg DP (2002). Bio-social origins of depression in the community. Interactions between social adversity, cortisol and serotonin neurotransmission. *British Journal of Psychiatry* 180, 168-73.
Targum SD (1984) Persistent neuroendocrine dysregulation in major depressive disorder: a marker for early relapse. *Biological Psychiatry* 19, 305-318.
Watson D, Pennebaker JW (1989) Health complaints, stress, and distress: Exploring the central role of negative affectivity. *Psychological Review* 96, 234-254.
Weinstock M (1997) Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neuroscience and Biobehavioral Reviews* 21, 1-10.
Williamson DE, Birmaher B, Anderson BP, al Shabbout M, Ryan ND (1995) Stressful life events in depressed adolescents: the role of dependent events during the depressive episode. *Journal of the American Academy of Child and Adolescent Psychiatry* 34, 591-598.
Zayas V, Shoda Y, Ayduk ON (2002) Personality in context: an interpersonal systems perspective. *Journal of Personality* 70, 851-900.
Zobel A, Barkow K, Schulze-Rauschenbach S, Von Widdern O, Metten M, Pfeiffer U, Schnell S, Wagner M, Maier W (2004) High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic-pituitary-adrenocortical system in healthy volunteers. *Acta Psychiatrica Scandinavica* 109, 392-399.
Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M (2001) Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. A prospective study. *Journal of Psychiatric Research* 35, 83-94.

8

Future research and clinical implications

In this chapter, some recommendations for future research will be given as well as some suggestions of possible implications for clinical practice.

FUTURE RESEARCH

One important conclusion drawn in Chapter 7 was that the present study has not elucidated how neuroticism increases risk of depression. In that chapter we suggested that it might be necessary to measure other factors than the ones we did or to measure them in a different way. With regard to social cognition, for example, we suggested that priming tasks might be more suitable to detect biases in emotion perception associated with neuroticism. Studying other *kinds* of processing biases might also be an option. It might prove useful to investigate cognitive operations that require more effortful elaboration, like the storage and retrieval of emotional information. Neuroticism has thus far been associated most frequently with biases in memory processes, especially in the recall of information relating to the self (Martin, 1985). Depression also has been associated more consistently with problems in elaborate cognitive functions than with problems in the passive early stages of information processing (Williams, 1997).

We still think it makes sense to try to explicate neuroticism by means of depression-related factors that are more tangible than a self-report score. Self-report neuroticism scores are useful as a quick and potent risk indicator, but they do not explain *why* neurotics are at increased risk, so they also cannot yield clues with regard to prevention. It is therefore important that future researchers more often use observational, informant, interview, and laboratory-based methods alongside the traditional self-report measures of neuroticism (cf. Klein et al., 2002; Ormel et al., 2004).

Apart from trying to clarify the concept of neuroticism by relating it to more objective risk factors and mechanisms, it might also be useful to parse the concept itself. Neuroticism is a higher-order personality dimension, which means that it is an assemblage of several lower-order traits ("facets"). The concept therefore is rather broad and non-specific - a "container concept". The majority of studies have examined neuroticism at the higher-order level. It might be that studying the underlying facets will provide more or different insights. There is evidence that only particular facets of neuroticism play a role in the development of depression (Klein et al., 2002), and that the mechan-

isms by which the various facets increase risk of depression may differ (Zuroff et al., 2004). It might also be easier to find cognitive, behavioral, or physiological correlates of neuroticism when the concept is studied at the level of facets (cf. Claridge and Davis, 2001).

Above, we recommended the use of other measures than self-report ones. One problem with such measures is that they are laborious and expensive. This is especially true for ethological assessments, i.e. systematic observations of nonverbal behavior. The author of this thesis and her assistants have spent many hours in front of a TV screen to register the nonverbal behaviors of the participants and their interviewers meticulously. We do think this undertaking has been worthwhile. Nonverbal behavior is an essential element of human communication, an element neglected too often by psychiatric researchers and clinicians. Our study has shown that nonverbal communication is also relevant with respect to the occurrence of stressful life events and recurrence of depression. These findings can be considered even more telling in view of the fact that we could not assess nonverbal communication in all its subtleties. For example, we registered the frequency and the duration of gaze (one of the elements of our involvement factor), but we did not account for the fact that people can look at each other in many different ways. Presumably, there have been several of such nonverbal nuances that we could not grasp with our instruments.

More research is required to reveal the exact role of nonverbal aspects of communication in recurrence of depression. It would be a great help when technology develops further so that the laborious work of the behavioral observations can be automated. Some promising advances in this direction have been made in recent years (e.g., Noldus et al., 2001; Grammer et al., 2002). A next step would be to study everyday interactions of former depressives, especially those with "significant others" like partners or close friends. There is reason to believe that disturbances in interpersonal behavior come to the surface especially in interactions with such significant others (Schmaling and Becker, 1991).

With respect to the study of stressful life events, our findings suggest that a simple questionnaire can be an adequate measure. Of course, interview-based methods like the LEDS are preferable, as they can provide additional contextual information (Brown and Harris, 1989). Such methods, however, are much more elaborate. A self-report questionnaire can be administered more easily, making it more feasible to collect the relevant information prospecti-

vely (cf. Ch 7, p. 149). One direction for future research would be to investigate more everyday types of interpersonal stress. Life events are very important in the context of depression, but they occur relatively infrequently. Minor experiences of interpersonal stress occur far more often (in some people's lives they occur every other day). It would be interesting to study such minor stressors: to investigate how neuroticism is related to them; how they are related to recurrence of depression (cf. Monroe and Harkness, 2005); and whether problems in nonverbal communication do indeed contribute to their occurrence, as we have assumed. One difficulty with such research is how to assess such stressors adequately. This difficulty probably also explains why many researchers prefer to study life events; life events are relatively clear-cut incidents, and their occurrence is therefore easier to establish (but see, for instance, Myin-Germeys et al., 2003, for a clever alternative).

One of our findings was that a positive association between cortisol levels and negative emotion perception was related to recurrence of depression. We interpreted this finding with reference to the notion of the hypersensitive fear circuit (Ch 7, pp.154-156). This finding definitely should be investigated more thoroughly. At any rate, our way of establishing it was rather indirect and not very elegant. A direction for future research may be to identify factors that can serve as a more direct measure for the degree to which the fear circuit is sensitized. It would also be interesting to do more research on the positive side of the sensitization coin; to investigate how such phenomena can be prevented or counteracted. Animal research has yielded some remarkable results in this respect. For example, whereas early, chronic, or repeated stress is known to result in long-lasting hypersensitivity of the HPA axis, increased maternal caregiving, induced by neonatal handling of rat pups, has been found to lead to a *decrease* in HPA-axis excitability. Rat pups reared in this way are less sensitive to stress and less fearful later in life (Weinstock, 1997; Heim and Nemeroff, 2001). In a similar vein, social housing of adult rats has been found to counteract the neuroendocrine effects of chronic stress exposure, especially in females (Westenbroek, 2004).

CLINICAL IMPLICATIONS

Of course, it would be naive to think that the results of the study can be translated directly into a clinical treatment strategy or a prevention program.

The distance between fundamental research and clinical practice is long. Moreover, one should be cautious when making causal inferences. One cannot be sure whether the risk factors identified in the present study are also *causal* factors. Establishing the causal influence of a factor on an outcome would imply to show that by manipulating the factor one could alter the outcome (Kraemer et al., 1997). We did not do so. Moreover, our results have to be replicated.

Nevertheless, the study does indicate some points of potential clinical importance. First, the findings suggest that some problems of individuals at risk of recurrence may only appear in the interplay between these individuals and others. This points to the relevance of an integrated treatment approach that focuses not only on the remitted patient but also on his or her social environment. This may especially be relevant in recurrent depression. When individuals become depressed over and over again, a great burden is also placed on families, partners, and friends. The result may be a progressive worsening of the interpersonal circumstances of the affected individuals (see Ch 7, p. 158). Interpersonal psychotherapy may do some good in this respect, as this type of therapy is specifically directed at improving the interpersonal problems of (former) depressives (Klerman and Weissmann, 1987; Frank et al., 1990).

Another point which the study hints at is the importance of nonverbal signals in interpersonal interactions. Clinical practitioners may benefit from paying more attention to nonverbal aspects of communication (Bouhuys, 2003; Philippot et al., 2003). For example, nonverbal cues may provide information of which clients are unaware, or information which they are unwilling or unable to report. Further, nonverbal communication is an important element in the creation and maintenance of the therapeutic relationship. Processes of nonverbal matching and synchronization like the one we studied are particularly relevant in this respect. Congruent body movements and mirror-imaged postures have been found to be linked to perceptions of affiliation and increased verbal disclosure (Cappella, 1981). Clinicians who are nonverbally "in tune" with their clients are more likely to induce feelings of rapport and relatedness in their clients and are more often perceived as being warm and understanding, which has been shown to contribute to the success of the therapeutic interaction (e.g., Davis and Hadiks, 1994; Van Os et al., 2005; Lambert and Barley, 2002). Nonverbal behavior may also be an explicit focus of therapy (Segrin, 2000; Philippot et al., 2003). Although nonverbal communi-

cation occurs largely unconsciously, it can be brought under conscious control. Training can help to increase patients' awareness of nonverbal signals and to teach them how to employ nonverbal behaviors in a more favorable way (e.g., Kinseth, 1989; Bellack et al., 1996). Such training has been found to be effective in the treatment of depression (Bellack et al., 1981; Hersen, 1984; Dow, 1994). It might also be useful in therapies aimed at preventing recurrence.

Our finding that a positive association between HPA-axis hyperactivity and negative emotion perception was related to recurrence of depression also requires some clinical considerations. The idea behind this finding was that the usual link between these systems may have become sensitized as a result of previous episodes of depression or of early or chronic stress exposure, in a way as proposed by stress-sensitization and cognitive kindling models of depression (Segal et al., 1996; Post and Weiss, 1998). Such sensitization processes do not have to be irredeemable. Above, we noted that animal research has shown the potential of some conditions (care, support) to prevent or counteract stress-induced alterations of the HPA axis. In humans, it has been shown that hypercortisolemia can be reduced by antiglucocorticoid treatment (Wolkowitz et al., 2001). Behavioral approaches aimed at decreasing stress and arousal (e.g., relaxation techniques and stress management therapies) have also been found to be effective in lowering cortisol levels (Wolkowitz et al., 2001). Such behavioral methods seem to be more favorable in the long run, as they increase the flexibility and adaptability of the stress system rather than "clamping" hormonal activity at a certain level (Wolkowitz et al., 2001). Cognitive kindling phenomena also are not necessarily irreversible. Cognitive therapy has proven quite successful in the treatment of depression as well as in preventing depression relapse and recurrence (Beck et al., 1985; Scott, 1996; Fava et al., 2003). It may also prove useful in adjusting biases in emotion perception like the ones found in our study. A combined approach, targeting both stress physiology and social cognition, might prove most effective in this respect.

REFERENCES

Beck AT, Rush AJ, Shaw BF, Emery G (1985) *Cognitive therapy of depression*. New York, NY: Guilford Press.

Bellack A, Hersen M, Himmelhoch J (1981) Social skills training compared with pharmacotherapy and psychotherapy in the treatment of unipolar depression. *American Journal of Psychiatry* 138, 1562-1567.

Bellack A, Hersen M, Himmelhoch J (1996) Social skills training for depression: A treatment manual. In *Sourcebook of psychological treatment manuals for adult disorders*, pp. 179-200. Eds V Van Hasselt and M Hersen. New York, NY: Plenum Press.

Bouhuys AL (2003) Ethology and depression. In *Nonverbal behavior in clinical settings*, pp. 233-262. Eds P Philippot, EJ Coats, and RS Feldman. London: Oxford University Press.

Brown GW, Harris TO (1989) *Life events and illness*. New York, NY: Guilford Press.

Cappella JN (1981) Mutual influence in expressive behavior: adult-adult and infant-adult dyadic interaction. *Psychological Bulletin* 89, 101-132.

Claridge G, Davis C (2001) What's the use of neuroticism? *Personality and Individual Differences* 31, 383-400.

Davis M, Hadiks D (1994) Nonverbal aspects of therapist attunement. *Journal of Clinical Psychology* 50, 393-405.

Dow M (1994) Social inadequacy and social skill. In *Cognitive and behavioral interventions: An empirical approach to mental health problems*, pp. 123-140. Eds L Craighead and WE Craighead. Needham Heights, MA: Allyn & Bacon.

Fava G, Ruini C, Sonino N (2003) Treatment of recurrent depression: A sequential psychotherapeutic and psychopharmacological approach. *CNS Drugs* 17(15), 1109-1117.

Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ (1990) Three-year outcomes for maintenance therapies in recurrent depression. *Archives of General Psychiatry* 47, 1093-1099.

Grammer K, Fink B, Renninger L (2002) Dynamic systems and inferential information processing in human communication. *Neuroendocrinology Letters* 23 Suppl 4, 15-22.

Heim C, Nemeroff CB (2001) The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry* 49, 1023-1039.

Hersen M, Bellack A, Himmelhoch J, Thase M (1984) Effects of social skill training, amitriptyline, and psychotherapy in unipolar depressed women. *Behavior Therapy* 15, 21-40.

Kinseth L (1989) Nonverbal training for psychotherapy: Overcoming barriers to clinical work with client nonverbal behavior. *Clinical Supervisor* 7, 5-25.

Klein DN, Durbin CE, Shankman SA, Santiago NJ (2002) Depression and personality. In

Handbook of depression, pp. 115-140. Eds IH Gotlib and CL Hammen. New York, NY: Guilford Press.

Klerman GL, Weissmann MM (1987) Interpersonal psychotherapy (IPT) and drugs in the treatment of depression. *Pharmacopsychiatry* 20, 3-7.

Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ (1997) Coming to terms with the terms of risk. *Archives of General Psychiatry* 54, 337-343.

Lambert M, Barley D (2002) Research summary on the therapeutic relationship and psychotherapy outcome. In *Psychotherapy relationships that work: Therapist contributions and responsiveness to patients*, pp. 17-32. Ed. J Norcross. London: Oxford University Press.

Martin M (1985). Neuroticism as predisposition toward depression: a cognitive mechanism. *Personality and Individual Differences* 6, 353-65.

Myin-Germeys I, Peeters F, Havermans R, Nicolson NA, DeVries MW, Delespaul P, Van Os J (2003) Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatrica Scandinavica* 107, 124-131.

Monroe SM, Harkness KL (2005) Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychological Review* 112, 417-445.

Noldus LP, Spink AJ, Tegelenbosch RA (2001) EthoVision: a versatile video tracking system for automation of behavioral experiments. *Behavior Research Methods, Instruments, and Computers* 33, 398-414.

Ormel J, Rosmalen J, Farmer A (2004) Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* 39, 906-912.

Philippot P, Feldman RS, Coats EJ (2003) The role of nonverbal behavior in clinical settings: introduction and overview. In *Nonverbal behavior in clinical settings*, pp. 3-13. Eds P Philippot, EJ Coats, and RS Feldman. London: Oxford University Press.

Post RM, Weiss SRB (1998) Sensitization and kindling phenomena in mood, anxiety, and obsessive-compulsive disorders: the role of serotonergic mechanisms in illness progression. *Biological Psychiatry* 44, 193-206.

Schmaling K, Becker J (1991) Empirical studies of the interpersonal relations of adult depressives. In *Psychosocial aspects of depression*, pp. 169-185. Eds J Becker and A Kleinman. Hillsdale, NJ: Lawrence Erlbaum Associates.

Scott J (1996) Cognitive therapy of affective disorders: a review. *Journal of Affective Disorders* 37, 1-11.

Segal ZV, Williams JM, Teasdale JD, Gemar M (1996) A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine* 26, 371-380.

Segrin C (2000) Social skills deficits associated with depression. *Clinical Psychology Review* 20, 379-403.

Van Os TWDP, Van den Brink RH, Tiemens BG, Jenner JA, Van der Meer K, Ormel J (2005) Communicative skills of general practitioners augment the effectiveness of guideline-based depression treatment. *Journal of Affective Disorders* 84, 43-51.

Weinstock M (1997) Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neuroscience and Biobehavioral Reviews* 21, 1-10.

Westenbroek C (2004) *Influence of gender and social environment in an animal model of affective disorders. Evidence for 'social support' in rats?* (Thesis). Groningen: University of Groningen.

Williams JMG, Watts FN, MacLeod C, Mathews A (1997). *Cognitive psychology and emotional disorders*. Chichester: Wiley.

Wolkowitz OM, Epel ES, Reus VI (2001) Stress hormone-related psychopathology: pathophysiological and treatment implications. *World Journal of Biological Psychiatry* 2, 115-143.

Zuroff DC, Mongrain M, Santor DA (2004) Conceptualizing and measuring personality vulnerability to depression: comment on Coyne and Whiffen (1995). *Psychological Bulletin* 130, 489-511.

Samenvatting

Depressie is een ingrijpende ziekte, onder andere vanwege haar sterk recidiverende karakter. Veel mensen die eenmaal depressief zijn geweest, worden dat vaker. Bovendien lijkt de kans op depressie groter te worden naarmate men meer episodes heeft meegemaakt. Het is dus van groot belang erachter te komen wat maakt dat de ziekte vaak (en steeds vaker) terugkomt.

Risicofactoren voor het ontwikkelen van depressie en voor recidief worden veelal geïsoleerd bestudeerd, ondanks het feit dat depressie een heterogeen verschijnsel is met een multifactoriële oorsprong. In het onderhavige proefschrift worden 5 verschillende soorten risicofactoren tegelijk onderzocht (factoren op het gebied van persoonlijkheid, sociale cognitie, interpersoonlijk gedrag, stressfysiologie en interpersoonlijke stress). Doel is na te gaan of deze factoren in hun onderlinge samenhang kunnen verklaren waarom mensen die hersteld zijn van een depressie opnieuw depressief worden.

Ons uitgangspunt daarbij is de persoonlijkheidsdimensie neuroticisme. Neuroticisme staat voor een verzameling met elkaar samenhangende trekken op het vlak van emotionele labiliteit, angstigheid, tobberigheid, somberheid en sensitiviteit. Het intrigerende aan dit brede persoonlijkheidsconcept is dat het op zeer consistente wijze samenhangt met depressie en allerlei andere vormen van misère. Onduidelijk is echter wat neuroticisme precies is en waaròm het zo'n consistente voorspeller is van psychiatrische problematiek en ander soort tegenslag. Deze studie is erop gericht dit vage concept wat handen en voeten te geven door het te relateren aan factoren uit de 4 andere onderzoeksgebieden. We verwachten dat elk van deze factoren een deel van het risico op depressie dat met neuroticisme gepaard gaat, kan verklaren.

De factoren van onze interesse zijn gekozen vanuit een interpersoonlijk

perspectief. Sociale factoren spelen een grote rol bij depressie, niet alleen bij het ontstaan ervan, vooral ook bij het herstel en het terugkeren van de ziekte. Wij verwachten dat interpersoonlijke mechanismen ook als verklaring kunnen dienen voor het verband tussen neuroticisme en depressie.

Op het gebied van *sociale cognitie* richten we ons op emotieperceptie. We kijken met name naar de manier waarop herstelde patiënten emoties uitgedrukt in gezicht en stem interpreteren. Het is bekend dat depressieve patiënten problemen hebben met emotieperceptie; ze maken er vaak fouten bij en vertonen een negatieve bias. Een negatieve kijk hebben op dingen is ook een van de aspecten die gevat worden onder neuroticisme. Wij verwachten dat een negatieve bias in emotieperceptie voorspellend is voor recidief en ook voor een deel kan verklaren waarom neuroticisme daar een risicofactor voor is.

Neuroticisme wordt over het algemeen opgevat als iets dat onder andere gereflecteerd wordt in gedrag (hoewel tot dusver niet zo duidelijk is in welk soort gedrag). In ons onderzoek kijken we naar *interpersoonlijk* gedrag, en dan vooral naar hoe mensen nonverbaal met elkaar communiceren. Nonverbale signalen zijn erg belangrijk in sociale interacties, al zijn mensen zich daar vaak niet zo van bewust. Vooral de manier waarop mensen hun nonverbale gedragingen op elkaar afstemmen lijkt van fundamenteel belang. Mensen hebben onbewust de neiging elkaars gedragingen te spiegelen en elkaars ritmes over te nemen. Dergelijke onwillekeurige imitatie- en synchronisatieprocessen komen vrij algemeen voor, ook al op heel jonge leeftijd, en blijken samen te hangen met de kwaliteit van sociale interacties. Interactiepartners die nonverbaal "op dezelfde golflengte zitten", ontlenen meer plezier en bevrediging aan de interactie en voelen zich meer tot elkaar aangetrokken. Nonverbale afstemming blijkt ook samen te hangen met een gunstiger verloop van de depressie. Wij verwachten dat de mate waarin herstelde patiënten en hun interactiepartners hun nonverbale gedrag op elkaar afstemmen ook voorspellend is voor recidief. Gebrekkige nonverbale afstemming kan mogelijk ook helpen verklaren waarom neurotische mensen een verhoogd risico op depressie hebben.

Een verhoogde gevoeligheid voor stress wordt door velen gezien als een kernelement van neuroticisme. Om die reden onderzoeken wij ook factoren op het gebied van de *stressfysiologie*. Onze aandacht gaat daarbij uit naar het zogenaamde "stresshormoon" cortisol. Veel depressieve patiënten hebben verhoogde cortisolniveaus, als gevolg van veranderingen in de hypothalamus-hypofyse-bijnieras (HPA-as). Hoewel dit hypercortisolisme gewoonlijk weer

verdwijnt zodra de depressie over is, zijn er ook mensen bij wie de HPA-as blijvende veranderingen vertoont. Bij deze mensen blijft het stress-systeem overgevoelig. Deze mensen lopen ook een hoger risico op het ontwikkelen van een volgende depressieve episode. Wij verwachten dat hoge cortisolniveaus bij herstelde patiënten een blijvend hyperactieve HPA-as reflecteren en daarom voorspellend zullen zijn voor recidief. We verwachten dat neuroticisme ook via deze weg tot depressie leidt.

Interpersoonlijke stress is een belangrijk concept in veel theorieën over depressie. Men meent dat het een grote rol speelt in het ontstaan, voortduren en terugkomen van de ziekte. Wij onderzoeken interpersoonlijke stress in de vorm van "ernstige levensgebeurtenissen". Dat zijn ingrijpende voorvallen die zo af en toe in het leven van mensen plaatsvinden. Ernstige levensgebeurtenissen zijn notoire triggers van depressie. Vooral ernstige levensgebeurtenissen in de interpersoonlijke sfeer, zoals een relatiecrisis of een sterfgeval in de familie, katalyseren het ontstaan van depressie. Neurotische mensen blijken meer ernstige levensgebeurtenissen mee te maken dan anderen. Wij verwachten dat het optreden van ernstige levensgebeurtenissen een mediërende factor is tussen neuroticisme en depressie, met name die gebeurtenissen waarbij interacties tussen mensen een rol spelen. Wij denken dat de manier waarop neuroticisme zich manifesteert in sociale cognitie, interpersoonlijk gedrag en stressfysiologie (zie boven) ook duidelijk zal kunnen maken waarom neurotische mensen meer van dit soort gebeurtenissen meemaken dan anderen.

Deelnemers aan dit onderzoek waren 104 patiënten uit het noorden van Nederland, poliklinisch behandeld voor unipolaire depressie of dysthymie. Deze patiënten werden onderworpen aan een uitgebreide basismeting aan het begin van het onderzoekstraject, op het moment dat de ziekte in remissie was. Deze meting bestond uit vragenlijsten, waarmee persoonlijkheidsaspecten in kaart werden gebracht, en computertaken, waarmee emotieperceptie werd gemeten. Ook werden tijdens deze meting video-opnames gemaakt van gesprekken tussen deelnemers en onderzoeksmedewerkers, waarmee nonverbale aspecten van communicatie konden worden geanalyseerd. De deelnemers verzamelden bovendien een etmaal lang hun urine, zodat cortisolniveaus konden worden bepaald. Na de basismeting werden de deelnemers 2 jaar lang gevolgd. Tijdens dit vervolgtraject werd in kaart gebracht welke ernstige levensgebeurtenissen de deelnemers overkwamen. Ook werd om de 4 weken een depressielijst afgenomen. Deelnemers die tweemaal achter elkaar boven

een kritieke waarde op die lijst scoorden, werden opgeroepen voor een diagnostisch interview waarmee kon worden nagegaan of er inderdaad sprake was van een recidief.

Hoofdstuk 1 dient als introductie op de 5 verschillende onderzoeksgebieden en de specifieke factoren waarop ons onderzoek zich richt. Besproken wordt wat er bekend is over de relatie tussen deze factoren en depressie en waarom te verwachten is dat deze factoren ook voorspellend zijn voor recidief. Daarna wordt ingegaan op de (mogelijke) relaties tussen deze factoren onderling. Op basis hiervan wordt een model opgesteld dat beschrijft hoe deze factoren in hun onderlinge samenhang kunnen verklaren hoe neuroticisme tot depressie leidt.

Hoofdstuk 2 doet verslag van een pilot-studie naar de voorspelling van recidief op basis van interpersoonlijk gedrag. Deze studie betreft een andere groep dan die de basis vormde voor de rest van het proefschrift. Het gaat hier om een relatief kleine groep patiënten die opgenomen is geweest in een kliniek (n = 51). Het vervolgtraject was in dit geval slechts 6 maanden. De basismeting vond plaats op het moment van ontslag. Tijdens deze meting werden video-opnames gemaakt van gesprekken tussen deelnemers en onderzoeksmedewerkers. Deze opnames werden geanalyseerd op nonverbale aspecten van communicatie. Met name nonverbale signalen die betrokkenheid bij de interactie weergeven werden onderzocht. Dit werd gedaan bij zowel de herstelde patiënten als bij hun gesprekspartners. Lage niveaus van betrokkenheid van de kant van de patiënten bleken samen te hangen met terugval na 6 maanden. De mate van afstemming tussen het nonverbale betrokkenheidsgedrag van de interactiepartners bleek níet voorspellend voor terugval. Dat laatste spoorde niet met onze verwachtingen.

De hoofdstukken 3 tot en met 6 gaan over het onderzoek gedaan met de onderzoeksgroep van poliklinisch behandelde patiënten (n = 104), met het vervolgtraject van 2 jaar.

Hoofdstuk 3 behandelt de vraag of er op het moment van de basismeting verschillen tussen individuen te vinden zijn op het gebied van persoonlijkheid, sociale cognitie en stressfysiologie, die te maken kunnen hebben met verschillen in ziekte*geschiedenis*. Mensen die al vaker een depressieve episode hebben doorgemaakt, verschillen mogelijk van mensen die nog maar één keer

depressief zijn geweest. Ze zouden hogere neuroticisme-scores, meer afwijkingen in emotieperceptie of hogere cortisolniveaus kunnen hebben. Er bleken in onze groep geen verschillen te bestaan in persoonlijkheid, maar wel in stressfysiologie en sociale cognitie. Mensen met een geschiedenis van recidiverende depressie hadden hogere cortisolniveaus dan mensen hersteld van een eerste episode. Vrouwen met een geschiedenis van recidiverende depressie waren bovendien negatiever in de perceptie van vocale expressies dan vrouwen met een eenmalige episode. De gevonden verschillen zouden de reden kunnen zijn *waarom* deze mensen al vaker een depressie hebben gehad ofwel daar een *gevolg* van kunnen zijn.

Hoofdstuk 4 gaat over de voorspelling van *toekomstig* recidief, en dan met name over de rol van cortisol en emotieperceptie daarbij. Speciale aandacht wordt besteed aan de emotie *angst*. Uit de literatuur is bekend dat cortisolsecretie en angstperceptie elkaar wederzijds beïnvloeden. Ook is bekend dat langdurige of herhaalde blootstelling aan hoge cortisolniveaus kan leiden tot permanente veranderingen in de neuronale verbindingen die deze relatie onderhouden. Als gevolg daarvan zouden cortisolsecretie en angstperceptie een excessieve invloed op elkaar kunnen gaan uitoefenen. Men denkt dat een dergelijk "overgevoelig angstcircuit" ten grondslag ligt aan diverse vormen van psychopathologie, waaronder depressie. De studie beschreven in hoofdstuk 4 laat zien dat in onze groep hoge cortisolniveaus en hoge niveaus van angstperceptie op zich niet voorspellend waren voor recidief. Het laatste gold zowel voor het horen van angst in vocale expressies als voor het zien van angst in gezichtsexpressies. Cortisol en angstperceptie bleken echter wel voorspellend voor recidief in interactie met elkaar. In overeenstemming hiermee was een ander soort analyse dat liet zien dat alleen bij mensen die later een recidief zouden krijgen er een positief verband bestond tussen cortisolniveaus en angstperceptie. Dit zou erop kunnen duiden dat er in deze mensen een versterkte link tussen cortisolsecretie en angstperceptie bestaat; een ondersteuning van de gedachte dat een overgevoelig angstcircuit het risico op recidief verhoogt.

In **Hoofdstuk 5** wordt opnieuw gekeken naar de voorspelling van recidief op basis van interpersoonlijk gedrag (zoals in hoofdstuk 2), maar nu in de grotere onderzoeksgroep en met het langere vervolgtraject. Bovendien wordt nu onderzocht hoe gedragsfactoren zich hierbij verhouden tot persoonlijkheidsfactoren. Net als in de studie van hoofdstuk 2 werd gefocust op nonverbale signalen die betrokkenheid bij de interactie weergeven. Op het

gebied van persoonlijkheid werd gekeken naar neuroticisme en extraversie. Zoals verwacht bleken deze beide persoonlijkheidsdimensies voorspellend voor recidief. Neuroticisme verhoogde de kans om opnieuw depressief te worden, extraversie verlaagde die kans. Ook nonverbaal betrokkenheidsgedrag bleek voorspellend voor recidief. In dit geval bleek het echter niet zozeer te gaan om hoge niveaus van betrokkenheid op zich, als wel om de mate waarin de gesprekspartners hun niveaus op elkaar afstemden. Hoe meer zij in dit opzicht op één lijn zaten, hoe kleiner de kans op recidief voor wat betreft de patiënt. Gebrekkige nonverbale afstemming bleek echter niet te kunnen verklaren waarom neuroticisme een risicofactor voor depressie is; beide soorten factoren waren onafhankelijk van elkaar voorspellend voor recidief.

In **Hoofdstuk 6** draait het om de vraag of het optreden van ernstige levensgebeurtenissen mogelijk een mediërende schakel is tussen gebrekkige nonverbale afstemming en recidief. De achterliggende gedachte is dat wanneer mensen tijdens sociale interacties nonverbaal niet goed op elkaar afgestemd raken, de kans groot is dat die interacties ongemakkelijk, onbevredigend of stressvol zullen zijn. Dit zou op de lange termijn ernstige levensgebeurtenissen in de interpersoonlijke sfeer, zoals een scheiding of een ingrijpend conflict, in de hand kunnen werken. Ernstige levensgebeurtenissen op hun beurt kunnen een trigger zijn voor depressie. De studie beschreven in hoofdstuk 6 laat zien dat een gebrekkige nonverbale afstemming tijdens het gesprek van de basismeting inderdaad bleek samen te hangen met een grotere blootstelling aan ernstige levensgebeurtenissen tijdens het vervolgtraject. Deze samenhang betrof alleen de "interpersoonlijke" levensgebeurtenissen, d.w.z. die levensgebeurtenissen waar –per definitie– interpersoonlijke interacties een rol in hadden kunnen gespeeld. Het optreden van dergelijke gebeurtenissen bleek een sterke voorspeller van recidief en bleek bovendien een mediërende factor tussen gebrekkige nonverbale afstemming en recidief.

In **Hoofdstuk 7** worden de bevindingen uit de voorgaande hoofdstukken geïntegreerd en geëvalueerd. Dit wordt gedaan aan de hand van het model dat in hoofdstuk 1 werd opgesteld. Dit model beschrijft hoe neuroticisme tot recidief kan leiden via de mediërende en modulerende effecten van de 4 andere soorten factoren (emotieperceptie, nonverbale communicatie, HPA-as-activatie en ernstige interpersoonlijke levensgebeurtenissen). Het model blijkt deels te worden bevestigd, deels ook niet. Onze poging om het diffuse concept neuroticisme te expliciteren door het te vertalen in concretere

factoren op het gebied van sociale cognitie, interpersoonlijk gedrag en stressfysiologie, strandde. Neuroticisme bleek zich niet te manifesteren in negatieve emotieperceptie, gebrekkige nonverbale communicatie of een hyperactieve HPA-as. Deze factoren konden (dus) ook niet verklaren waarom neurotische mensen vaker een ernstige levensgebeurtenis meemaken en waarom ze vaker een recidief ontwikkelen. Wel in overeenstemming met het model was het idee dat gebrekkige nonverbale communicatie bijdraagt aan het optreden van ernstige interpersoonlijke levensgebeurtenissen en op die manier de kans op recidief vergroot. Ook de verwachting dat een hyperactieve HPA-as en een negatieve bias in emotieperceptie elkaar versterken en op die wijze het risico op recidief verhogen, bleek uit te komen. Lós van elkaar bleken deze factoren echter niet voorspellend voor recidief. Al met al leverde het onderzoek beschreven in dit proefschrift ons dus enig inzicht op in de interpersoonlijke mechanismen die maken dat mensen die hersteld zijn van een depressie opnieuw depressief worden. Het vertelde ons echter niet waarom neurotische mensen dat vaker doen dan anderen.

Hoofdstuk 8 gaat in op de mogelijke implicaties van onze bevindingen voor toekomstig onderzoek en klinische praktijk. Een suggestie voor toekomstige onderzoekers die meer grip willen krijgen op neuroticisme is dat het zinvol zou kunnen zijn om dit brede concept uiteen te leggen in de onderliggende facetten waaruit het is samengesteld. Een hint voor mensen in de klinische praktijk is dat er reden lijkt te zijn om (meer) aandacht te besteden aan nonverbale aspecten van communicatie.

Nawoord

Dit proefschrift is in hoge mate het werk van meerdere personen. Ten eerste waren er de mensen die, koud bekomen van een depressie, bereid waren deel te nemen aan dit onderzoek. De behandelaars en het ondersteunend personeel van GGZ Acute Zorg Leeuwarden (regio Harlingen) hielpen ons bij het werven van de deelnemers en maakten het mogelijk ze ter plaatse te onderzoeken. Met name aan Titus van Os hebben we wat dat betreft een hoop te danken. Freek Veneman en Minke Plat waren een geweldige hulp bij de logistiek van het onderzoek en bij het contact met de cliënten. In het UMCG in Groningen hielpen de behandelaars en secretaresses van de polikliniek en de deeldagbehandeling ons bij de werving van deelnemers. Rento Heins bleek daarbij van grote waarde. In een later stadium hebben wij ook de mogelijkheid gekregen deelnemers te werven onder de cliënten van de overige regio's van GGZ Acute Zorg Leeuwarden en onder die van GGZ Acute Zorg Drachten, GGZ Acute Zorg Sneek, CGG Winschoten, CGG Delfzijl, CGG Stadskanaal en GGZ Drenthe. Alle betrokkenen wil ik bedanken voor hun medewerking.

Het zal menig lezer zijn opgevallen dat ik in dit proefschrift meestal de 1e persoon meervoud gebruik. Dat is omdat er van meet af aan een groepje mensen bij dit onderzoeksproject betrokken is geweest, te weten Netty Bouhuys, Erwin Geerts, Ingrid van der Spoel en Titus van Os. De samenwerking met deze mensen was zeer intensief. Dat heeft er toe geleid dat ik me aan het eind echt moest forceren om het woord "ik" te gebruiken bij het schrijven. Daar ben ik daarom ook maar weer mee opgehouden. De begeleiding van Netty was bijzonder in vele opzichten. Haar betrokkenheid bij mijn project was groot en ik kon altijd bij haar binnenvallen. Vooral haar begrip en steun in het laatste jaar hebben veel indruk op me gemaakt. Erwin was groots in

zijn collegialiteit, humor en incasseringsvermogen. Onze opvattingen en denkwijzen wilden nog wel eens botsen. Het feit dat dit nooit op een echte ruzie is uitgelopen is vermoedelijk vooral aan zijn persoon te danken. Ingrid was, naast een leuk mens, mijn steun op praktisch gebied. Zij deed ook een groot deel van de interviews en onderhield het contact met de deelnemers, en dat op een zeer prettige manier. Titus was behalve erg goed voor mijn steekproefgrootte ook erg goed voor mijn humeur. Om een of andere reden werd ik altijd blij als ik hem zag. In een later stadium van het onderzoek heb ik veel gehad aan prof. Hans Ormel. Met zijn snelle, adequate commentaar op mijn stukken heb ik een hoop voordeel kunnen doen. Ik was vooral gecharmeerd van het feit dat hij zijn kritiek steeds op zo'n manier bracht dat ik het gevoel had zelf nog te kunnen beslissen of ik er wat mee deed of niet.

Nog een aantal andere mensen leverde een bijdrage aan dit onderzoek. Prof. Tom Snijders was van grote waarde met zijn advies op methodologisch gebied. Ik stond keer op keer versteld van zijn vermogen om in zeer korte tijd mijn probleem te doorgronden, het te vertalen in statistiek en vervolgens te komen met een creatieve oplossing. Prof. Wiebo Brouwer maakte het ons mogelijk aan te haken bij de ontwikkeling van de prosodietest, waar zijn groep op dat moment mee bezig was. Marieke Pijnenborg was daar ook bij betrokken. Zij hielp mij later als stagiaire bij de verwerking van een deel van de prosodiegegevens. Twee andere stagiaires die me hielpen waren Sjoerd Dijkema, die een deel van de videobanden 'scoorde', en Nynke Dijkema, die de gegevens over het medicatiegebruik en de ernstige levensgebeurtenissen invoerde.

In de laatste maanden hebben diverse mensen een bijdrage geleverd aan de redactie en de vormgeving van het proefschrift. Kees Bos, Hansa Krijgsman, Coralie Velleman, Daan Bos en Jos Horst hebben stukken tekst onder handen gehad. Ingrid van der Spoel, inmiddels carrière makend als natuurfotograaf, zette een vaag idee van mij om in een doeltreffende foto voor de voorkant. Manon Vrieling gaf het proefschrift prachtig vorm, daarbij goed aanvoelend wat ik wilde. Manon geeft trouwens vorm zoals ze voetbalt.

De professoren Beersma, Bouma en Van Os waren bereid het proefschrift te lezen, als leden van de beoordelingscommissie. Dank daarvoor.

Zonder 'een leven ernaast' had ik dit proefschrift niet kunnen schrijven. Daarom een paar woorden over de mensen die dit leven mogelijk en aangenaam maakten. Op de afdeling Sociale Psychiatrie waren dat de vele collega's

met wie ik lol kon hebben en bij wie ik mijn hart kon luchten. Een speciale vermelding verdienen Liesbeth Lindeboom (Linde*bos* voor mij want veel meer dan 1 boom), Marieke de Groot (met wie ik Werkte aan de Grenzen van het Weten), Henk Jan Conradi (zolang we niet over politiek praatten konden we prima door 1 draaideur), Herman Kluiter ('als het zó moet!'), Sjoerd Sytema ('als ik jou zie, moet ik huilen') en Esther Holthausen. Natuurlijk moet ook Sietse Dijk vermeld worden, die voor m'n gevoel zo'n 40.000 artikelen voor me heeft opgezocht. Sietse kon ook altijd aan mijn hoofd zien wanneer ik weer een werkbespreking had gehad. Daarnaast ben ik erg blij geweest met de mensen die op de donderdagmiddag onder lunchtijd wilden volleyballen; dit wekelijkse sportuurtje heeft zeer bijgedragen aan mijn welzijn, vooral omdat ik er altijd zo enorm bij moest lachen.

Een collega die al snel veel meer dan een collega werd, was Jan Neeleman. Jan maakte mijn verhuizing naar het barre Groningen gemakkelijk door mij reeds vanaf de eerste weken te overstelpen met een grote hoeveelheid liefde. Daarnaast kwam hij, met zijn onmetelijke brein, op het spoor van een diagnose. Daarmee voorkwam hij misschien wel een voortijdig einde van mijn loopbaan.

Een andere collega die al snel een speciale plaats veroverde in mijn gemoed was Laura Batstra. Sinds ik Laura ken heb ik het idee dat het leven een soort stripverhaal is. Vermoedelijk komt dat door haar bijzondere kijk op de dingen, haar vermogen de humor en absurditeit ervan in te zien, en haar vaardigheid dat ook nog eens mooi te verwoorden. Ik mocht mijn hoofd ook altijd vrijelijk aan haar (niet onaanzienlijke) boezem drukken, hetgeen ik menigmaal gedaan heb en nog vaak hoop te doen. Misschien al wel tijdens de promotieplechtigheid, wanneer zij mijn paranimf zal zijn.

Karin de Geeter zal mijn andere paranimf zijn. Dat is niet alleen vanwege haar geweldige organisatietalent. Karin is in mijn Groninger jaren ook een goede vriendin geworden waarmee het erg prettig op de bank zitten en chocola eten is, zeker in tijden van emotionele toestanden.

Indirect relevant voor het kunnen afronden van dit proefschrift is de voetbalclub DIVA geweest; een heerlijke sport, een merkwaardig maar geweldig stel vrouwen.

Aan mijn ouders Kees en Riek heb ik zeer veel te danken. Een van die dingen was hun belofte dat ik altijd kon langskomen om hen een poot uit te draaien als ik in financiële problemen zou raken. Het is jammer dat dat uiteindelijk niet nodig is gebleken, aangezien mijn broers en zus in de tussentijd

mijn erfdeel aan het opsouperen zijn geweest met hun vele fantastische - doch bodemloze - projecten. Die broers en die zus (en de leuke types met wie zij hebben aangepapt) zijn niettemin erg fijn om te hebben.

Groningen heeft mij veel bijzonders gebracht, waaronder Jos Horst. Jos liet me zien dat met een frisbee gooien veel leuker is als er ook iemand is om 'm naar toe te gooien. De laatste jaren is deze man langzaam maar zeker in mijn hele systeem doorgedrongen. Hij is de centrale verwarming.

Groningen, september 2005.

Curriculum vitae

Elisabeth Henriëtte (Elske) Bos werd op 20 december 1970 geboren te Zwolle. In 1989 deed zij eindexamen Gymnasium ß aan het Carolus Clusius College te Zwolle. Daarna begon zij met de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. Na het afronden van de propedeuse van deze studie (1990) verhuisde zij voor een half jaar naar Zuid-Frankrijk om koeien te melken. Vervolgens woonde en werkte zij een half jaar met verstandelijk gehandicapte kinderen in een instituut in Noord-Ierland. In 1991 keerde zij terug naar de Vrije Universiteit, ditmaal om Biologie en Wijsbegeerte te gaan studeren. De studie Biologie rondde zij in 1995 cum laude af, met als hoofdrichtingen neurobiologie, gedragsbiologie en theoretische biologie. Het doctoraal Wijsbegeerte behaalde zij in 1998 (cum laude), met als specialisaties wijsgerige ethiek en wijsgerige antropologie. Gedurende de jaren 1997 en 1998 werkte zij als onderzoeksassistent bij de vakgroep Theoretische Biologie aan de Vrije Universiteit te Amsterdam. Daarna werkte zij in dezelfde stad als docent biologie aan het Amstellyceum en als fietsenmaker bij De Fietsenmaker. In 1999 verhuisde zij naar Groningen om als AIO aan de slag te gaan bij de Medische Faculteit van de Rijksuniversiteit Groningen, disciplinegroep Psychiatrie. Hier schreef zij het onderhavige proefschrift. In de jaren 2002 en 2003 combineerde zij haar onderzoekswerk met fietsenmaken bij Cycle Shop Fietsen te Groningen, in afwachting van de follow-up gegevens van het onderzoek. In 2004 hing zij de steeksleutels weer aan de wilgen teneinde haar proefschrift af te ronden.